10/018308

```
Welcome to DIALOG

Dialog level 04.20.00D

Last logoff:  26jan05 15:57:51
Logon file405 01feb05 17:09:43
           *** ANNOUNCEMENT ***
                    ***
--Important Notice to Freelance Authors--
See HELP FREELANCE for more information
                    ***
NEW FILES RELEASED
***German Patents Fulltext (File 324)

***Beilstein Abstracts (File 393)
***Beilstein Facts (File 390)
***Beilstein Reactions (File 391)
                    ***
UPDATING RESUMED
Medline (Files 154 & 155)

                    ***
REMOVED
***Info Sci & Tech Abs (File 202)
***Internet & Personal Comp Abs (File 233)
***CanCorp Financials (File 491)
     >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
     >>>    of new databases, price changes, etc.      <<<
                    ****
* * *
SYSTEM:HOME
Cost is in DialUnits
Menu System II: D2 version 1.7.9 term=ASCII
                      *** DIALOG HOMEBASE(SM) Main Menu ***

 Information:
  1.  Announcements (new files, reloads, etc.)
  2.  Database, Rates, & Command Descriptions
  3.  Help in Choosing Databases for Your Topic
  4.  Customer Services (telephone assistance, training, seminars, etc.)
  5.  Product Descriptions

 Connections:
  6.  DIALOG(R) Document Delivery
  7.  Data Star(R)

    (c) 2003 Dialog, a Thomson business.      All rights reserved.

      /H = Help            /L = Logoff          /NOMENU = Command Mode


Enter an option number to view information or to connect to an online
 service.  Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
?
Terminal set to DLINK
                    *** DIALOG HOMEBASE(SM) Main Menu ***
```

```
 Information:
  1.  Announcements (new files, reloads, etc.)
  2.  Database, Rates, & Command Descriptions
  3.  Help in Choosing Databases for Your Topic
  4.  Customer Services (telephone assistance, training, seminars, etc.)
  5.  Product Descriptions

 Connections:
  6.  DIALOG(R) Document Delivery
  7.  Data Star(R)

    (c) 2003 Dialog, a Thomson business.      All rights reserved.

      /H = Help            /L = Logoff          /NOMENU = Command Mode


Enter an option number to view information or to connect to an online
 service.  Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
? b 411

       01feb05 17:09:50 User276646 Session D73.1
            $0.00    0.206 DialUnits FileHomeBase
     $0.00  Estimated cost FileHomeBase
     $0.02  TELNET
     $0.02  Estimated cost this search
     $0.02  Estimated total session cost   0.206 DialUnits

File 411:DIALINDEX(R)

DIALINDEX(R)
   (c) 2005 The Dialog Corporation

*** DIALINDEX search results display in an abbreviated ***
*** format unless you enter the SET DETAIL ON command. ***
? sf allscience
   You have 287 files in your file list.
   (To see banners, use SHOW FILES command)
? s (isoflavonoid or isoflavone or isoflavonoids or isoflavones or
dihydroisoflavone or daidzein or genistein or glycitein) and (prodrug or
prodrugs or pro()drug or pro()drugs)

Your SELECT statement is:
   s (isoflavonoid or isoflavone or isoflavonoids or isoflavones or
dihydroisoflavone or daidzein or genistein or glycitein) and (prodrug or
prodrugs or pro()drug or pro()drugs)

          Items   File
          -----   ----
              8     5: Biosis Previews(R)_1969-2005/Jan W3
              1     9: Business & Industry(R)_Jul/1994-2005/Jan 31
              1    15: ABI/Inform(R)_1971-2005/Feb 01
              4    16: Gale Group PROMT(R)_1990-2005/Feb 01
              3    20: Dialog Global Reporter_1997-2005/Feb 01
              9    34: SciSearch(R) Cited Ref Sci_1990-2005/Jan W4
              1    35: Dissertation Abs Online_1861-2005/Jan
```

```
          2    50: CAB Abstracts_1972-2004/Dec
          4    71: ELSEVIER BIOBASE_1994-2005/Jan W4
         10    73: EMBASE_1974-2005/Jan W4
          3    94: JICST-EPlus_1985-2005/Dec W3
Examined  50 files
          1   107: Adis R&D Insight_1986-2005/Jan W4
          3   135: NewsRx Weekly Reports_1995-2005/Jan W4
          4   144: Pascal_1973-2005/Jan W4
          6   148: Gale Group Trade & Industry DB_1976-2005/Jan 31
          1   149: TGG Health&Wellness DB(SM)_1976-2005/Jan W4
          8   155: MEDLINE(R)_1951-2005/Jan W5
          5   156: ToxFile_1965-2005/Dec W4
          2   162: Global Health_1983-2005/Dec
          1   172: EMBASE Alert_2005/Jan W4
Examined 100 files
          1   211: Gale Group Newsearch(TM)_2005/Jan 31
          4   324: German National Patents_1980-2005/Week 01
         22   340: CLAIMS(R)/US Patent_1950-05/Jan 27
          1   345: Inpadoc/Fam.& Legal Stat_1968-2004/UD=200504
Examined 150 files
         26   348: EUROPEAN PATENTS_1978-2005/Jan W03
        365   349: PCT FULLTEXT_1979-2002/UB=20050127,UT=20050120
          2   357: Derwent Biotech Res.__1982-2005/Jan W5
         10   390: Beilstein Facts_ July 2004
          1   391: Beilstein Reactions_ July 2004
          5   399: CA SEARCH(R)_1967-2005/UD=14206
         34   440: Current Contents Search(R)_1990-2005/Feb 01
          1   441: ESPICOM Pharm&Med DEVICE NEWS_2005/Jan W4
          1   452: Drug Data Report_1992-2005/Dec
          5   453: Drugs of the Future_1990-2002/Oct
          3   484: Periodical Abs Plustext_1986-2005/Jan W4
Examined 200 files
          4   545: Investext(R)_1982-2005/Feb 01
          1   553: Wilson Bus. Abs. FullText_1982-2004/Sep
          3   610: Business Wire_1999-2005/Feb 01
          3   621: Gale Group New Prod.Annou.(R)_1985-2005/Feb 01
          1   635: Business Dateline(R)_1985-2005/Feb 01
          2   636: Gale Group Newsletter DB(TM)_1987-2005/Feb 01
          3   649: Gale Group Newswire ASAP(TM)_2005/Jan 25
        430   654: US Pat.Full._1976-2005/Jan 27
Examined 250 files
          1   759: Business Insights_1992-2005/Jan
          1   761: Datamonitor Market Res._1992-2005/Jan

   45 files have one or more items; file list includes 287 files.

? rf
Your last SELECT statement was:
   S (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES OR DIHYDR-
OISOFLAVONE OR DAIDZEIN OR GENISTEIN OR GLYCITEIN) AND (PRODRUG OR PRODRUGS
 OR PRO()DRUG OR PRO()DRUGS)
Ref        Items   File
---        -----   ----
N1           430   654: US Pat.Full._1976-2005/Jan 27
N2           365   349: PCT FULLTEXT_1979-2002/UB=20050127,UT=20050120
N3            34   440: Current Contents Search(R)_1990-2005/Feb 01
N4            26   348: EUROPEAN PATENTS_1978-2005/Jan W03
```

```
N5             22   340: CLAIMS(R)/US Patent_1950-05/Jan 27
N6             10    73: EMBASE_1974-2005/Jan W4
N7             10   390: Beilstein Facts_ July 2004
N8              9    34: SciSearch(R) Cited Ref Sci_1990-2005/Jan W4
N9              8     5: Biosis Previews(R)_1969-2005/Jan W3
N10             8   155: MEDLINE(R)_1951-2005/Jan W5
   45 files have one or more items; file list includes 287 files.

        - Enter P or PAGE for more -
? b n1:n45
       01feb05 17:13:52 User276646 Session D73.2
           $18.08    7.232 DialUnits File411
    $18.08  Estimated cost File411
     $1.33  TELNET
    $19.41  Estimated cost this search
    $19.43  Estimated total session cost   7.437 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File 654:US Pat.Full. 1976-2005/Jan 27
         (c) Format only 2005 The Dialog Corp.
  File 349:PCT FULLTEXT 1979-2002/UB=20050127,UT=20050120
         (c) 2005 WIPO/Univentio
  File 440:Current Contents Search(R) 1990-2005/Feb 01
         (c) 2005 Inst for Sci Info
  File 348:EUROPEAN PATENTS 1978-2005/Jan W03
         (c) 2005 European Patent Office
  File 340:CLAIMS(R)/US Patent 1950-05/Jan 27
         (c) 2005 IFI/CLAIMS(R)
*File 340: 2004 Reload is online as of October 6, 2004.  Pricing
changes effective October 1, 2004.  See HELP NEWS 340 for details.
  File  73:EMBASE 1974-2005/Jan W4
         (c) 2005 Elsevier Science B.V.
*File  73: Price change effective Jan 1, 2005. Enter HELP
RATES 73 for details.
  File 390:Beilstein Facts  July 2004
         (c) 2004 Beilstein GmbH
*File 390: File has been reloaded. Please see HELP NEWS 390.
IMPORTANT - Price based on output.  See HELP RATES 390.
  File  34:SciSearch(R) Cited Ref Sci 1990-2005/Jan W4
         (c) 2005 Inst for Sci Info
*File  34: Price change effective Jan 1, 2005. Enter HELP
RATES 34 for details.
  File   5:Biosis Previews(R) 1969-2005/Jan W3
         (c) 2005 BIOSIS
*File   5: Price change effective Jan 1, 2005. Enter HELP
RATES 5 for details.
  File 155:MEDLINE(R) 1951-2005/Jan W5
         (c) format only 2005 The Dialog Corp.
*File 155: Medline has resumed updating. Please see
HELP NEWS 155 for details.
  File 148:Gale Group Trade & Industry DB 1976-2005/Jan 31
         (c)2005 The Gale Group
*File 148: Alert feature enhanced for multiple files, duplicate
removal, customized scheduling. See HELP ALERT.
  File 156:ToxFile 1965-2005/Dec W4
         (c) format only 2005 The Dialog Corporation
```

***File 156: Updating of ToxFile has resumed, with**
UD=20041205.
File 399:CA SEARCH(R) 1967-2005/UD=14206
(c) 2005 American Chemical Society
***File 399: Use is subject to the terms of your user/customer agreement.**
Alert feature enhanced for multiple files, etc. See HELP ALERT.
File 453:Drugs of the Future 1990-2002/Oct
(c) 2002 Prous Science
***File 453: Updating of this file has temporarily ceased due to**
a production system change.
File 16:Gale Group PROMT(R) 1990-2005/Feb 01
(c) 2005 The Gale Group
***File 16: Alert feature enhanced for multiple files, duplicate**
removal, customized scheduling. See HELP ALERT.
File 71:ELSEVIER BIOBASE 1994-2005/Jan W4
(c) 2005 Elsevier Science B.V.
File 144:Pascal 1973-2005/Jan W4
(c) 2005 INIST/CNRS
***File 144: Price change effective Jan 1, 2005. Enter HELP**
RATES 144 for details.
File 324:German National Patents 1980-2005/Week 01
(c) 2004 Univentio
***File 324: Search original German text plus English translation.**
For further information, enter HELP NEWS 324.
File 545:Investext(R) 1982-2005/Feb 01
(c) 2005 Thomson Financial Networks
File 20:Dialog Global Reporter 1997-2005/Feb 01
(c) 2005 The Dialog Corp.
File 94:JICST-EPlus 1985-2005/Dec W3
(c)2005 Japan Science and Tech Corp(JST)
File 135:NewsRx Weekly Reports 1995-2005/Jan W4
(c) 2005 NewsRx
***File 135: New newsletters are now added. See Help News135 for the**
complete list of newsletters.
File 484:Periodical Abs Plustext 1986-2005/Jan W4
(c) 2005 ProQuest
***File 484: SELECT IMAGE AVAILA**BILITY FOR PROQUEST FILES
ENTER 'HELP PROQUEST' FOR MORE
File 610:Business Wire 1999-2005/Feb 01
(c) 2005 Business Wire.
***File 610: File 610 now contains data from 3/99 forward.**
Archive data (1986-2/99) is available in File 810.
File 621:Gale Group New Prod.Annou.(R) 1985-2005/Feb 01
(c) 2005 The Gale Group
File 649:Gale Group Newswire ASAP(TM) 2005/Jan 25
(c) 2005 The Gale Group
File 50:CAB Abstracts 1972-2004/Dec
(c) 2005 CAB International
File 162:Global Health 1983-2005/Dec
(c) 2005 CAB International
File 357:Derwent Biotech Res. _1982-2005/Jan W5
(c) 2005 Thomson Derwent & ISI
File 636:Gale Group Newsletter DB(TM) 1987-2005/Feb 01
(c) 2005 The Gale Group
File 9:Business & Industry(R) Jul/1994-2005/Jan 31
(c) 2005 The Gale Group
File 15:ABI/Inform(R) 1971-2005/Feb 01

```
        (c) 2005 ProQuest Info&Learning
*File  15: Alert feature enhanced for multiple files, duplicate
removal, customized scheduling. See HELP ALERT.
  File  35:Dissertation Abs Online 1861-2005/Jan
        (c) 2005 ProQuest Info&Learning
  File 107:Adis R&D Insight 1986-2005/Jan W4
        (c) 2005 Adis Data Information BV.
  File 149:TGG Health&Wellness DB(SM) 1976-2005/Jan W4
        (c) 2005 The Gale Group
  File 172:EMBASE Alert 2005/Jan W4
        (c) 2005 Elsevier Science B.V.
*File 172: Price change effective Jan 1, 2005. Enter HELP
RATES 172 for details.
  File 211:Gale Group Newsearch(TM) 2005/Jan 31
        (c) 2005 The Gale Group
  File 345:Inpadoc/Fam.& Legal Stat 1968-2004/UD=200504
        (c) 2005 EPO
  File 391:Beilstein Reactions  July 2004
        (c) 2004 Beilstein GmbH
  File 441:ESPICOM Pharm&Med DEVICE NEWS 2005/Jan W4
        (c) 2005 ESPICOM Bus.Intell.
  File 452:Drug Data Report 1992-2005/Dec
        (c) 2005 Prous Science
  File 553:Wilson Bus. Abs. FullText 1982-2004/Sep
        (c) 2004 The HW Wilson Co
  File 635:Business Dateline(R) 1985-2005/Feb 01
        (c) 2005 ProQuest Info&Learning
  File 759:Business Insights 1992-2005/Jan
        (c) 2005 Datamonitor
  File 761:Datamonitor Market Res. 1992-2005/Jan
        (c) 2005 Datamonitor

      Set  Items  Description
      ---  -----  -----------
? s (isoflavonoid or isoflavone or isoflavonoids or isoflavones or
dihydroisoflavone or daidzein or genistein or glycitein) and (prodrug or
prodrugs or pro()drug or pro()drugs)
Processing
Processed  10 of  45 files ...
Processing
Processed  30 of  45 files ...
Completed processing all files
           6711  ISOFLAVONOID
          26405  ISOFLAVONE
           8307  ISOFLAVONOIDS
          33818  ISOFLAVONES
             12  DIHYDROISOFLAVONE
          13332  DAIDZEIN
          50392  GENISTEIN
           1766  GLYCITEIN
          98751  PRODRUG
          86862  PRODRUGS
        2735721  PRO
       15188610  DRUG
          13125  PRO(W)DRUG
        2735721  PRO
        4477753  DRUGS
```

```
            8607  PRO(W)DRUGS
      S1    1007  (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR
                  ISOFLAVONES OR DIHYDROISOFLAVONE OR DAIDZEIN OR GENISTEIN
                  OR GLYCITEIN) AND (PRODRUG OR PRODRUGS OR PRO()DRUG OR
                  PRO()DRUGS)
? s s1 and dt=review
>>>One or more prefixes are unsupported
>>>  or undefined in one or more files.
            1007  S1
         3214815  DT=REVIEW
      S2       3  S1 AND DT=REVIEW
? rd
>>>Duplicate detection is not supported for File 654.
>>>Duplicate detection is not supported for File 349.
>>>Duplicate detection is not supported for File 348.
>>>Duplicate detection is not supported for File 340.
>>>Duplicate detection is not supported for File 390.
>>>Duplicate detection is not supported for File 453.
>>>Duplicate detection is not supported for File 324.
>>>Duplicate detection is not supported for File 107.
>>>Duplicate detection is not supported for File 345.
>>>Duplicate detection is not supported for File 391.
>>>Duplicate detection is not supported for File 441.
>>>Duplicate detection is not supported for File 452.
>>>Duplicate detection is not supported for File 759.
>>>Duplicate detection is not supported for File 761.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S3       3  RD (unique items)
? d s3/3/1-3
      Display 3/3/1     (Item 1 from file: 73)
DIALOG(R)File  73:EMBASE
(c) 2005 Elsevier Science B.V. All rts. reserv.

12792619     EMBASE No: 2004380132
  Nanoparticle and targeted systems for cancer therapy
  Brannon-Peppas L.; Blanchette J.O.
  L. Brannon-Peppas, Department of Biomedical Engineering, The University
  of Texas at Austin, 1 Univ. Station, C0800, 78712-0231, Austin, TX
  United States
  AUTHOR EMAIL: peppas@mail.utexas.edu
  Advanced Drug Delivery Reviews ( ADV. DRUG DELIV. REV. ) (Netherlands)
22 SEP 2004, 56/11 (1649-1659)
  CODEN: ADDRE   ISSN: 0169-409X
  PUBLISHER ITEM IDENTIFIER: S0169409X04001450
  DOCUMENT TYPE: Journal ;  Review
  LANGUAGE: ENGLISH   SUMMARY LANGUAGE: ENGLISH
  NUMBER OF REFERENCES: 43

                                  - end of record -
?

      Display 3/3/2     (Item 2 from file: 73)
DIALOG(R)File  73:EMBASE
(c) 2005 Elsevier Science B.V. All rts. reserv.
```

10926447 EMBASE No: 1998327168
Etoposide: Four decades of development of a topoisomerase II inhibitor
Hande K.R.
K.R. Hande, Vanderbilt Univ. School of Medicine, Department of Medical Oncology, Nashville VA Medical Center, Nashville, TN United States
European Journal of Cancer (EUR. J. CANCER) (United Kingdom) 1998, 34/10 (1514-1521)
CODEN: EJCAE ISSN: 0959-8049
PUBLISHER ITEM IDENTIFIER: S0959804998002287
DOCUMENT TYPE: Journal; **Review**
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 76

- end of record -

?

Display 3/3/3 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

05836989 EMBASE No: 1994256680
Recent advances in anti-HIV agents
Rane D.F.; Dasmahapatra B.; Schwartz J.
Schering-Plough Research Institute, 2015 Galloping Hill Road,Kenilworth, NJ 07033 United States
Expert Opinion on Therapeutic Patents (EXPERT OPIN. THER. PAT.) (United Kingdom) 1994, 4/8 (941-955)
CODEN: EOTPE ISSN: 1354-3776
DOCUMENT TYPE: Journal; **Review**
LANGUAGE: ENGLISH

- end of record -

? d s3/7/1-3
>>>Format 7 is not valid in file 759
>>>Format 7 is not valid in file 761
Display 3/7/1 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

12792619 EMBASE No: 2004380132
Nanoparticle and targeted systems for cancer therapy
Brannon-Peppas L.; Blanchette J.O.
L. Brannon-Peppas, Department of Biomedical Engineering, The University of Texas at Austin, 1 Univ. Station, C0800, 78712-0231, Austin, TX United States
AUTHOR EMAIL: peppas@mail.utexas.edu
Advanced Drug Delivery Reviews (ADV. DRUG DELIV. REV.) (Netherlands) 22 SEP 2004, 56/11 (1649-1659)
CODEN: ADDRE ISSN: 0169-409X
PUBLISHER ITEM IDENTIFIER: S0169409X04001450
DOCUMENT TYPE: Journal ; **Review**
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 43

This review explores recent work directed towards more targeted treatment of cancer, whether through more specific anti-cancer agents or through methods of delivery. These areas include delivery by avoiding the

reticuloendothelial system, utilizing the enhanced permeability and retention effect and tumor-specific targeting. Treatment opportunities using antibody-targeted therapies are summarized. The ability to treat cancer by targeting delivery through angiogenesis is also discussed and antiangiogenic drugs in clinical trials are presented. Delivery methods that specifically use nanoparticles are also highlighted, including both degradable and nondegradable polymers. (c) 2004 Elsevier B.V. All rights reserved.

- end of record -

?

Display 3/7/2 (Item 2 from file: 73)

10926447 EMBASE No: 1998327168

Etoposide: Four decades of development of a topoisomerase II inhibitor

Hande K.R.
K.R. Hande, Vanderbilt Univ. School of Medicine, Department of Medical Oncology, Nashville VA Medical Center, Nashville, TN United States

European Journal of Cancer (EUR. J. CANCER) (United Kingdom) 1998, 34/10 (1514-1521)
CODEN: EJCAE ISSN: 0959-8049
PUBLISHER ITEM IDENTIFIER: S0959804998002287
DOCUMENT TYPE: Journal; **Review**
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 76

Podophyllin-containing materials have been used as folk medicines for centuries. In the 1950s, scientists began a search to identify a more effective podophyllotoxin derivative. These efforts eventually resulted in the development of a new class of antineoplastic agents which targets the DNA unwinding enzyme, topoisomerase II. The history of the development of one of the first identified topoisomerase II inhibitors, etoposide, is reviewed in this paper. Critical developments in etoposide's mechanism of action, pharmacology and administration schedule are summarised. The clinical benefits of the recently marketed etoposide **prodrug** , etoposide phosphate (Etopophos(R)) are also detailed. The current status of other clinically approved anticancer agents which target topoisomerase II is briefly reviewed.

- end of record -

?

Display 3/7/3 (Item 3 from file: 73)

05836989 EMBASE No: 1994256680

Recent advances in anti-HIV agents

Rane D.F.; Dasmahapatra B.; Schwartz J.
Schering-Plough Research Institute, 2015 Galloping Hill Road,Kenilworth, NJ 07033 United States

Expert Opinion on Therapeutic Patents (EXPERT OPIN. THER. PAT.) (United Kingdom) 1994, 4/8 (941-955)
CODEN: EOTPE ISSN: 1354-3776

DOCUMENT TYPE: Journal; **Review**
LANGUAGE: ENGLISH

- end of record -

?

? d s3/9/3
Display 3/9/3 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

05836989 EMBASE No: 1994256680
Recent advances in anti-HIV agents
Rane D.F.; Dasmahapatra B.; Schwartz J.
Schering-Plough Research Institute, 2015 Galloping Hill Road,Kenilworth, NJ 07033 United States
Expert Opinion on Therapeutic Patents (EXPERT OPIN. THER. PAT.) (United Kingdom) 1994, 4/8 (941-955)
CODEN: EOTPE ISSN: 1354-3776
DOCUMENT TYPE: Journal; **Review**
LANGUAGE: ENGLISH
BRAND NAME/MANUFACTURER NAME: l 735524/merck; azt; azidothymidine; bch 189; ro 31 8959
MANUFACTURER NAMES: burroughs wellcome; rhone poulenc rorer; glaxo; janssen ; upjohn; merck; hoechst; smith kline and french; lilly; schering corporation; cyanamid; pfizer; marion merrell dow
DRUG DESCRIPTORS:
*antivirus agent--adverse drug reaction--ae; *antivirus agent--drug combination--cb; *antivirus agent--pharmacokinetics--pk; *antivirus agent --drug therapy--dt; *antivirus agent--drug development--dv
1,3 dioxolane derivative--drug development--dv; zalcitabine--adverse drug reaction--ae; zalcitabine--drug therapy--dt; didanosine--adverse drug reaction--ae; didanosine--drug therapy--dt; 2',3' dideoxynucleoside derivative--drug development--dv; 2',3' dideoxynucleoside derivative --adverse drug reaction--ae; 2',3' dideoxynucleoside derivative--drug therapy--dt; acyclic nucleoside--drug development--dv; alpha interferon --drug therapy--dt; alpha interferon--drug combination--cb; benzodiazepine derivative--drug development--dv; benzoxazinone derivative; ethylene derivative--drug development--dv; ethylene derivative--clinical trial--ct; ethylene derivative--drug therapy--dt; **isoflavonoid** --drug development--dv ; indinavir--clinical trial--ct; indinavir--drug development--dv; indinavir --drug therapy--dt; indinavir--pharmacokinetics--pk; lamivudine--drug therapy--dt; lamivudine--adverse drug reaction--ae; lamivudine--clinical trial--ct; saquinavir--clinical trial--ct; saquinavir--drug therapy--dt; nevirapine--drug development--dv; nucleoside analog--drug development--dv; piperazine derivative--drug development--dv; **prodrug** --drug development --dv; proteinase inhibitor--drug development--dv; pyridone derivative --clinical trial--ct; pyridone derivative--drug development--dv; pyridone derivative--drug therapy--dt; pyridone derivative--pharmacokinetics--pk; quinazoline; quinoline--drug development--dv; quinoxaline derivative; rna directed dna polymerase inhibitor--drug development--dv; rna directed dna polymerase inhibitor--drug therapy--dt; stavudine--adverse drug reaction --ae; stavudine--drug therapy--dt; stavudine--clinical trial--ct; thymidine derivative--drug therapy--dt; thymidine derivative--adverse drug reaction --ae; thymidine derivative--clinical trial--ct; unindexed drug; zidovudine --drug therapy--dt; zidovudine--drug combination--cb; zidovudine derivative --drug development--dv

```
MEDICAL DESCRIPTORS:
*human immunodeficiency virus infection--drug therapy--dt; *human
immunodeficiency virus infection--therapy--th; *human immunodeficiency
virus infection--prevention--pc; *human immunodeficiency virus infection
--etiology--et
acquired immune deficiency syndrome--therapy--th; acquired immune
deficiency syndrome--drug therapy--dt; acquired immune deficiency syndrome
--etiology--et; acquired immune deficiency syndrome--prevention--pc;
antiviral activity; bone marrow toxicity--side effect--si; clinical trial;
drug bioavailability; drug design; drug structure; gene therapy; human;
peripheral neuropathy--side effect--si; review; structure activity relation
; t lymphocyte
CAS REGISTRY NO.: 7481-89-2 (zalcitabine); 69655-05-6 (didanosine);
    150378-17-9, 157810-81-6 (indinavir); 134678-17-4, 134680-32-3 (
    lamivudine); 127779-20-8 (saquinavir); 129618-40-2 (nevirapine);
    37205-61-1 (proteinase inhibitor); 694-85-9 (pyridone derivative);
    253-82-7 (quinazoline); 91-22-5 (quinoline); 3056-17-5 (stavudine);
    30516-87-1 (zidovudine)
SECTION HEADINGS:
  004  Microbiology: Bacteriology, Mycology, Parasitology and Virology
  026  Immunology, Serology and Transplantation
  030  Clinical and Experimental Pharmacology
  037  Drug Literature Index
  038  Adverse Reaction Titles

                                  - end of record -
? ds

Set     Items   Description
S1       1007   (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES
             OR DIHYDROISOFLAVONE OR DAIDZEIN OR GENISTEIN OR GLYCITEIN) -
            AND (PRODRUG OR PRODRUGS OR PRO()DRUG OR PRO()DRUGS)
S2          3   S1 AND DT=REVIEW
S3          3   RD (unique items)
? s (prodrug or prodrugs) and dt=review
>>>One or more prefixes are unsupported
>>>  or undefined in one or more files.
          98751  PRODRUG
          86862  PRODRUGS
        3214815  DT=REVIEW
      S4    4867  (PRODRUG OR PRODRUGS) AND DT=REVIEW
? s s4 and (DAIDZEIN OR GENISTEIN OR GLYCITEIN)
           4867  S4
          13332  DAIDZEIN
          50392  GENISTEIN
           1766  GLYCITEIN
      S5       2  S4 AND (DAIDZEIN OR GENISTEIN OR GLYCITEIN)
? rd
>>>Duplicate detection is not supported for File 654.
>>>Duplicate detection is not supported for File 349.
>>>Duplicate detection is not supported for File 348.
>>>Duplicate detection is not supported for File 340.
>>>Duplicate detection is not supported for File 390.
>>>Duplicate detection is not supported for File 453.
>>>Duplicate detection is not supported for File 324.
>>>Duplicate detection is not supported for File 107.
>>>Duplicate detection is not supported for File 345.
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>>>Duplicate detection is not supported for File 391.
>>>Duplicate detection is not supported for File 441.
>>>Duplicate detection is not supported for File 452.
>>>Duplicate detection is not supported for File 759.
>>>Duplicate detection is not supported for File 761.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S6       2  RD (unique items)
? d s6/3/1-2
      Display 6/3/1     (Item 1 from file: 73)
DIALOG(R)File  73:EMBASE
(c) 2005 Elsevier Science B.V. All rts. reserv.

12792619     EMBASE No: 2004380132
  Nanoparticle and targeted systems for cancer therapy
  Brannon-Peppas L.; Blanchette J.O.
  L. Brannon-Peppas, Department of Biomedical Engineering, The University
  of Texas at Austin, 1 Univ. Station, C0800, 78712-0231, Austin, TX
  United States
  AUTHOR EMAIL: peppas@mail.utexas.edu
  Advanced Drug Delivery Reviews ( ADV. DRUG DELIV. REV. ) (Netherlands)
22 SEP 2004, 56/11 (1649-1659)
  CODEN: ADDRE   ISSN: 0169-409X
  PUBLISHER ITEM IDENTIFIER: S0169409X04001450
  DOCUMENT TYPE: Journal ;  Review
  LANGUAGE: ENGLISH   SUMMARY LANGUAGE: ENGLISH
  NUMBER OF REFERENCES: 43

                                - end of record -
?

      Display 6/3/2     (Item 2 from file: 73)
DIALOG(R)File  73:EMBASE
(c) 2005 Elsevier Science B.V. All rts. reserv.

10926447     EMBASE No: 1998327168
  Etoposide: Four decades of development of a topoisomerase II inhibitor
  Hande K.R.
  K.R. Hande, Vanderbilt Univ. School of Medicine, Department of Medical
  Oncology, Nashville VA Medical Center, Nashville, TN  United States
  European Journal of Cancer ( EUR. J. CANCER ) (United Kingdom)  1998,
  34/10 (1514-1521)
  CODEN: EJCAE   ISSN: 0959-8049
  PUBLISHER ITEM IDENTIFIER: S0959804998002287
  DOCUMENT TYPE: Journal;  Review
  LANGUAGE: ENGLISH   SUMMARY LANGUAGE: ENGLISH
  NUMBER OF REFERENCES: 76

                                - end of record -
? d ds
>>>No matching display code(s) found in file(s): 9, 15-16, 20, 34-35, 50,
   71, 73, 94, 107, 135, 144, 148-149, 155-156, 162, 172, 211, 324, 340,
   357, 390-391, 399, 440-441, 452-453, 484, 545, 553, 610, 621, 635-636,
   649, 654, 759, 761
? ds
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Set     Items   Description
S1       1007   (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES
             OR DIHYDROISOFLAVONE OR DAIDZEIN OR GENISTEIN OR GLYCITEIN) -
            AND (PRODRUG OR PRODRUGS OR PRO()DRUG OR PRO()DRUGS)
S2          3   S1 AND DT=REVIEW
S3          3   RD (unique items)
S4       4867   (PRODRUG OR PRODRUGS) AND DT=REVIEW
S5          2   S4 AND (DAIDZEIN OR GENISTEIN OR GLYCITEIN)
S6          2   RD (unique items)
? s (DAIDZEIN OR GENISTEIN OR GLYCITEIN)(10n)(prodrug or prodrugs)
           13332  DAIDZEIN
           50392  GENISTEIN
            1766  GLYCITEIN
           98751  PRODRUG
           86862  PRODRUGS
      S7      74  (DAIDZEIN OR GENISTEIN OR GLYCITEIN)(10N)(PRODRUG OR
                  PRODRUGS)
? rd
>>>Duplicate detection is not supported for File 654.
>>>Duplicate detection is not supported for File 349.
>>>Duplicate detection is not supported for File 348.
>>>Duplicate detection is not supported for File 340.
>>>Duplicate detection is not supported for File 390.
>>>Duplicate detection is not supported for File 453.
>>>Duplicate detection is not supported for File 324.
>>>Duplicate detection is not supported for File 107.
>>>Duplicate detection is not supported for File 345.
>>>Duplicate detection is not supported for File 391.
>>>Duplicate detection is not supported for File 441.
>>>Duplicate detection is not supported for File 452.
>>>Duplicate detection is not supported for File 759.
>>>Duplicate detection is not supported for File 761.

>>>Records from unsupported files will be retained in the RD set.
>>>Record 440:16392299 ignored; incomplete bibliographic data, not retained
 in RD set
...examined 50 records  (50)
...completed examining records
      S8      66  RD (unique items)
? ds

Set     Items   Description
S1       1007   (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES
             OR DIHYDROISOFLAVONE OR DAIDZEIN OR GENISTEIN OR GLYCITEIN) -
            AND (PRODRUG OR PRODRUGS OR PRO()DRUG OR PRO()DRUGS)
S2          3   S1 AND DT=REVIEW
S3          3   RD (unique items)
S4       4867   (PRODRUG OR PRODRUGS) AND DT=REVIEW
S5          2   S4 AND (DAIDZEIN OR GENISTEIN OR GLYCITEIN)
S6          2   RD (unique items)
S7         74   (DAIDZEIN OR GENISTEIN OR GLYCITEIN)(10N)(PRODRUG OR PRODR-
              UGS)
S8         66   RD (unique items)
? s s8 and (cancer)
              66  S8
         5607774  CANCER
      S9      48  S8 AND (CANCER)
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? d s9/3/1-10
      Display 9/3/1     (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005876291 **IMAGE Available
Derwent Accession: 2004-832455
Tyrosine kinase inhibitors as an adjunctive therapy to botulinum toxin
treatment
Inventor: Bonner, Philip Hallinger, INV
          Baker, Roberts, INV
          Radmanesh, Shardan Marc, INV
          Richardson, William Wallace, INV
Correspondence Address: STOCKWELL & ASSOCIATES, PSC, 861 CORPORATE DRIVE,
    SUITE 201, LEXINGTON, KY, 40503, US

               Publication                          Application    Filing
                  Number      Kind    Date           Number        Date
              --------------  --  --------  --------------  --------
Main Patent   US 20040228872  A1  20041118  US 2004784028   20040221
Provisional                                 US 60-449243    20030221


Fulltext Word Count: 5976

                                  - end of record -
? ds

Set     Items   Description
S1       1007   (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES
            OR DIHYDROISOFLAVONE OR DAIDZEIN OR GENISTEIN OR GLYCITEIN) -
           AND (PRODRUG OR PRODRUGS OR PRO()DRUG OR PRO()DRUGS)
S2          3   S1 AND DT=REVIEW
S3          3   RD (unique items)
S4       4867   (PRODRUG OR PRODRUGS) AND DT=REVIEW
S5          2   S4 AND (DAIDZEIN OR GENISTEIN OR GLYCITEIN)
S6          2   RD (unique items)
S7         74   (DAIDZEIN OR GENISTEIN OR GLYCITEIN)(10N)(PRODRUG OR PRODR-
           UGS)
S8         66   RD (unique items)
S9         48   S8 AND (CANCER)
? d s3/3/1-48
      Display 3/3/1     (Item 1 from file: 73)
DIALOG(R)File  73:EMBASE
(c) 2005 Elsevier Science B.V. All rts. reserv.

12792619     EMBASE No: 2004380132
  Nanoparticle and targeted systems for cancer therapy
  Brannon-Peppas L.; Blanchette J.O.
  L. Brannon-Peppas, Department of Biomedical Engineering, The University
  of Texas at Austin, 1 Univ. Station, C0800, 78712-0231, Austin, TX
  United States
  AUTHOR EMAIL: peppas@mail.utexas.edu
  Advanced Drug Delivery Reviews ( ADV. DRUG DELIV. REV. ) (Netherlands)
22 SEP 2004, 56/11 (1649-1659)
  CODEN: ADDRE   ISSN: 0169-409X
  PUBLISHER ITEM IDENTIFIER: S0169409X04001450
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DOCUMENT TYPE: Journal ; **Review**
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 43

- end of record -

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Display 3/3/2 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

10926447 EMBASE No: 1998327168
Etoposide: Four decades of development of a topoisomerase II inhibitor
Hande K.R.
K.R. Hande, Vanderbilt Univ. School of Medicine, Department of Medical Oncology, Nashville VA Medical Center, Nashville, TN United States
European Journal of Cancer (EUR. J. CANCER) (United Kingdom) 1998, 34/10 (1514-1521)
CODEN: EJCAE ISSN: 0959-8049
PUBLISHER ITEM IDENTIFIER: S0959804998002287
DOCUMENT TYPE: Journal; **Review**
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 76

- end of record -

? d s9/3/1-48
Display 9/3/1 (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.

0005876291 **IMAGE Available
Derwent Accession: 2004-832455
Tyrosine kinase inhibitors as an adjunctive therapy to botulinum toxin treatment
Inventor: Bonner, Philip Hallinger, INV
Baker, Roberts, INV
Radmanesh, Shardan Marc, INV
Richardson, William Wallace, INV
Correspondence Address: STOCKWELL & ASSOCIATES, PSC, 861 CORPORATE DRIVE, SUITE 201, LEXINGTON, KY, 40503, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20040228872	A1	20041118	US 2004784028	20040221
Provisional				US 60-449243	20030221

Fulltext Word Count: 5976

- end of record -

?

Display 9/3/2 (Item 2 from file: 654)
DIALOG(R)File 654:US Pat.Full.

0005764162
Derwent Accession: 2003-403281
PSMA formulations and uses thereof
Inventor: Maddon, Paul, INV
Donovan, Gerald, INV
Olson, William, INV
Schulke, Norbert, INV
Gardner, Jason, INV
Ma, Dangshe, INV
Correspondence Address: Janice A. Vatland Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20040161776	A1	20040819	US 2003695667	20031027
CIP	PENDING			US 2003395894	20030321
CIP	PENDING			WO 2002US33944	20021023
Provisional				US 60-335215	20011023
Provisional				US 60-362747	20020307
Provisional				US 60-412618	20020920

Fulltext Word Count: 59611

- end of record -

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Display 9/3/3 (Item 3 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005594411 **IMAGE Available
Derwent Accession: 2004-282455
Human sarcoma-associated antigens
Inventor: Scanlan, Matthew, INV
Lee, Sang-Yull, INV
Old, Lloyd, INV
Correspondence Address: WOLF GREENFIELD & SACKS, PC FEDERAL RESERVE PLAZA, 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2211, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20040063101	A1	20040401	US 2002260708	20020930

Fulltext Word Count: 36266

- end of record -

?

Display 9/3/4 (Item 4 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005542794 **IMAGE Available

Derwent Accession: 2003-403281
PSMA antibodies and protein multimers
Inventor: Maddon, Paul, INV
Donovan, Gerald, INV
Olson, William, INV
Schulke, Norbert, INV
Gardner, Jason, INV
Ma, Dangshe, INV
Correspondence Address: WOLF GREENFIELD & SACKS, PC FEDERAL RESERVE PLAZA, 600 ATLANTIC AVENUE, BOSTON, MA, 02210-2211, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20040033229	A1	20040219	US 2003395894	20030321
CIP	PENDING			WO 2002US33944	20021023
Provisional				US 60-335215	20011023
Provisional				US 60-362747	20020307
Provisional				US 60-412618	20020920

Fulltext Word Count: 64640

- end of record -

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Display 9/3/5 (Item 5 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005473342 **IMAGE Available
Derwent Accession: 2004-053036
Methods of treatment of glaucoma and other conditions mediated by NOS-2 expression via inhibition of the EGFR pathway
Inventor: Neufeld, Arthur, INV
Liu, Bin, INV
Assignee: Washington University 02)
Correspondence Address: SONNENSCHEIN NATH & ROSENTHAL LLP, P.O. BOX 061080 WACKER DRIVE STATION, SEARS TOWER, CHICAGO, IL, 60606-1080, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030232741	A1	20031218	US 2003430527	20030506
Provisional				US 60-378254	20020506

Fulltext Word Count: 14835

- end of record -

?

Display 9/3/6 (Item 6 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

5452088 **IMAGE Available

Derwent Accession: 1997-154039
Utility
C/ **Prophylactic and therapeutic treatment of the ductal epithelium of a mammary gland for** cancer
; CONTAC **TING THE DUCTAL EPITHELIUM OF THE EXOCRINE GLAND WITH EPITHELIUM DESTROYING AGENTS SUCH AS ETHANOL AND VACCINIA VIRUS**
Inventor: Sukumar, Saraswati Vaidyanathan, Columbia, MD
Assignee: Johns Hopkins University School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Nguyen, Dave T. (Art Unit: 163)
Law Firm: Leydig, Voit and Mayer, Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6656918	A	20031202	US 2000746588	20001221
Division	US 6330472	A		US 99240206	19990129
Division	US 5763415	A		US 96692001	19960802
Continuation	US 6153184	A		US 9893145	19980608

Fulltext Word Count: 5951

- end of record -

?
Display 9/3/7 (Item 7 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005448310 **IMAGE Available
Derwent Accession: 2002-668396
Means and methods for treatment evaluation
Inventor: Kuyl, Antoinette, INV
Cornelissen, Marion, INV
Correspondence Address: TRASK BRITT, P.O. BOX 2550, SALT LAKE CITY, UT, 84110, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030219772	A1	20031127	US 2002310677	20021205
CIP	PENDING			US 200255728	20020123
Provisional				US 60-325722	20010928

Fulltext Word Count: 17968

- end of record -

?
Display 9/3/8 (Item 8 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005377836
Derwent Accession: 2003-843953
Inhibition of muscle regeneration following myectomy
Inventor: Baker, Robert, INV

Bonner, Philip, INV
Radmanesh, Shardan, INV
Correspondence Address: Stockwell & Associates, PSC, Suite 201 861 Corporate Drive, Lexington, KY, 40503, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030181510	A1	20030925	US 2003392649	20030319
Provisional				US 60-365886	20020319

Fulltext Word Count: 5852

- end of record -

?

Display 9/3/9 (Item 9 from file: 654)

DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005376624 **IMAGE Available
Derwent Accession: 2003-075624
Cancer **-testis antigens**
Inventor: Old, Lloyd, INV
Nakayama, Eiichi, INV
Ono, Toshiro, INV
Assignee: Ludwig Institute for Cancer Research 02), New York, NY
Correspondence Address: John R. Van Amsterdam, Ph.D. Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030180298	A1	20030925	US 2002262666	20021001
CIP	PENDING			WO 2002US12497	20020419
Provisional				US 60-356937	20020214
Provisional				US 60-285343	20010420

Fulltext Word Count: 53625

- end of record -

?

Display 9/3/10 (Item 10 from file: 654)

DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005359785 **IMAGE Available
Derwent Accession: 2002-668396
Means and methods for treatment evaluation
Inventor: van der Kuyl, Antoinette, INV
Cornelissen, Marion, INV
Correspondence Address: TRASK BRITT, P.O. BOX 2550, SALT LAKE CITY, UT, 84110, US

	Publication Number	Kind	Date	Application Number	Filing Date

Main Patent	US 20030170720	A1	20030911	US 200255728	20020123
Provisional				US 60-325722	20010928
Priority				EP 2001200228	20010123
				EP 200120373	20010928

Fulltext Word Count: 14685

- end of record -

?

Display 9/3/11 (Item 11 from file: 654)

DIALOG(R)File 654:US Pat.Full.

0005226040

Derwent Accession: 2001-137633

Redox-stable, non-phosphorylated cyclic peptide inhibitors of SH2 domain binding to target protein, conjugates thereof, compositions and methods of synthesis and use

Inventor: Peter Roller, INV
Ya-Qiu Long, INV
Feng-Di Lung, INV
C. King, INV
Dajun Yang, INV

Assignee: The Govt. of the United States of America 02), Rockville, MD, 20852, Suite 325 6011 Executive Boulevard

Correspondence Address: LEYDIG VOIT & MAYER, LTD, TWO PRUDENTIAL PLAZA, SUITE 4900 180 NORTH STETSON AVENUE, CHICAGO, IL, 60601-6780, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030078368	A1	20030424	US 2001998350	20011130
CIP	PENDING			WO 2000US15201	20000602
Provisional				US 60-137187	19990602

Fulltext Word Count: 10554

- end of record -

?

Display 9/3/12 (Item 12 from file: 654)

DIALOG(R)File 654:US Pat.Full.

0005170494

Derwent Accession: 2003-708293

Formulations of tocopherols and methods of making and using them

Inventor: Guy Miller, INV
Lesley Brown, INV

Correspondence Address: Gladys H. Monroy Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA, 94304-1018, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030022818	A1	20030130	US 2002188587	20020702

Continuation	US 6426362	US 2000684588	20001006
Provisional		US 60-158234	19991008

Fulltext Word Count: 30592

- end of record -

?

Display 9/3/13 (Item 13 from file: 654)

DIALOG(R)File 654:US Pat.Full.

0005060047

Derwent Accession: 2002-472947

Pharmaceutical preparations comprising soybean isoflavone extracts and probiotic microogranisms

Inventor: Pierre Fabre, INV
Rene Belle, INV
Bernard Fabre, INV

Correspondence Address: THE FIRM OF HUESCHEN AND SAGE, 500 COLUMBIA PLAZA 350 EAST MICHIGAN AVENUE, KALAMAZOO, MI, 49007, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20020114786	A1	20020822	US 2001951690	20010914
Priority				FR 200011515	20000911

Fulltext Word Count: 3744

- end of record -

?

Display 9/3/14 (Item 14 from file: 654)

DIALOG(R)File 654:US Pat.Full.

0004980735 **IMAGE Available

Derwent Accession: 1997-154039

Prophylactic and therapeutic treatment of the ductal epithelium of a mammary gland for cancer

Inventor: Saraswati Sukumar, INV

Assignee: Johns Hopkins University School of Medicine 02), Baltimore, MD, 21202, US, 111 Market Place Suite 906

Correspondence Address: LEYDIG VOIT & MAYER, LTD, TWO PRUDENTIAL PLAZA, SUITE 4900 180 NORTH STETSON AVENUE, CHICAGO, IL, 60601-6780, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20020035356	A1	20020321	US 2001971901	20011005
Division	PENDING			US 99240206	19990129
Division	US 5763415			US 96692001	19960802
Continuation	US 6153184			US 9893145	19980608
Provisional				US 60-28929	19950803

Fulltext Word Count: 8424

- end of record -

?

Display 9/3/15 (Item 15 from file: 654)

DIALOG(R)File 654:US Pat.Full.

0004910718 **IMAGE Available

Derwent Accession: 1997-154039

Prophylactic and therapeutic treatment of the ductal epithelium of a mammary gland for cancer

Inventor: Saraswati Sukumar, INV

Correspondence Address: LEYDIG VOIT & MAYER, LTD, TWO PRUDENTIAL PLAZA, SUITE 4900 180 NORTH STETSON AVENUE, CHICAGO, IL, 60601-6780, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20010021701	A1	20010913	US 2000746588	20001221
Division	PENDING			US 99240206	19990129
Division	US 5763415			US 96692001	19960802
Continuation	US 6153184			US 9893145	19980608
Provisional				US 60-28929	19950803

Fulltext Word Count: 8426

- end of record -

?

Display 9/3/16 (Item 16 from file: 654)

DIALOG(R)File 654:US Pat.Full.

0004894533 **IMAGE Available

Derwent Accession: 1997-154039

new-utility

DESTRUCTION OF THE EPITHELIUM OF AN EXOCRINE GLAND IN THE PROPHYLACTIC AND THERAPEUTIC TREATMENT OF CANCER

Inventor: SARASWATI VAIDYANATHAN SUKUMAR, INV

Correspondence Address: CAROL LARCHER LEYDIG VOIT & MAYER, TWO PRUDENTIAL PLAZA SUITE 4900 180 NORTH STETSON, CHICAGO, IL, 606016780

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20010005505	A1	20010628	US 99240206	19990129
Continuation	US 6153184			US 9893145	19980608

Fulltext Word Count: 8426

- end of record -

?

Display 9/3/17 (Item 17 from file: 654)

DIALOG(R)File 654:US Pat.Full.

4868394 **IMAGE Available
Derwent Accession: 1997-154039
Utility
C/ **Destruction of the epithelium of an exocrine gland in the prophylactic and therapeutic treatment of** cancer
; CONTAC **TING THE DUCTAL EPITHELIUM OF MAMMARY GLAND BY DUCTAL CANNULATION WITH A VECTOR COMPRISING A GENE ENCODING A CYTOTOXIC GENE PRODUCT, WHICH, UPON TRANSFORMATION OF A CELL OF THE DUCTAL EPITHELIUM IT IS DESTROYED AND TUMORS INHIBITED**
Inventor: Sukumar, Saraswati Vaidyanathan, Columbia, MD
Assignee: Johns Hopkins University School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Nguyen, Dave T. (Art Unit: 163)
Law Firm: Leydig, Voit & Mayer Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6559130	A	20030506	US 2000634483	20000808
Division	US 6153184	A		US 9893145	19980608
Division	US 5763415	A		US 96692001	19960802

Fulltext Word Count: 5824

- end of record -

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Display 9/3/18 (Item 18 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

4721503
Derwent Accession: 2002-654874
Utility
REASSIGNED
C/ **Formulations of tocopherols and methods of making and using them**
; **RELIEVING CELL STRESS; SYNERGISTIC MIXTURE WITH FLAVONOIDS, TRANSFERRIN**
Inventor: Miller, Guy, Mountain View, CA
Brown, Lesley A., Cupertino, CA
Assignee: Galileo Laboratories, Inc. 02), Santa Clara, CA
Galileo Laboratories Inc (Code: 46759)
Examiner: Fay, Zohreh (Art Unit: 164)
Assistant Examiner: Kwon, Brian-Yong
Law Firm: Morrison & Foerster LLP

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6426362	A	20020730	US 2000684588	20001006

Fulltext Word Count: 27860

- end of record -

?

Display 9/3/19 (Item 19 from file: 654)
DIALOG(R)File 654:US Pat.Full.

4692037
Derwent Accession: 2000-442512
Utility
C/ **Method for the prophylactic treatment of cataracts ; GENISTEIN**
Inventor: de Juan, Jr., Eugene, Phoenix, MD
Assignee: Johns Hopkins University, School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Fay, Zohreh (Art Unit: 164)
Law Firm: Leydig, Voit & Mayer, Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6399655	A	20020604	US 98218956	19981222

Fulltext Word Count: 5488

- end of record -

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Display 9/3/20 (Item 20 from file: 654)
DIALOG(R)File 654:US Pat.Full.

4615679 **IMAGE Available
Derwent Accession: 1997-154039
Utility
E/ **Prophylactic and therapeutic treatment of the ductal epithelium for a mammary gland for** cancer
Inventor: Sukumar, Saraswati Vaidyanathan, Columbia, MD
Assignee: Johns Hopkins University School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Nguyen, Dave T. (Art Unit: 163)
Law Firm: Leydig, Voit & Mayer, Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6330472	A	20011211	US 99240206	19990129
Division	US 5763415	A	19980609	US 96692001	19960802
Continuation	US 6153184	A		US 9893145	19980608
Provisional				US 60-28929	19950803

Fulltext Word Count: 2710

- end of record -

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Display 9/3/21 (Item 21 from file: 654)

DIALOG(R)File 654:US Pat.Full.

4420667
Derwent Accession: 1997-154039
Utility
C/ **Destruction of the epithelium of an exocrine gland in the prophylactic and therapeutic treatment of** cancer
; CONTAC **TING, BY DUCTAL CANNULATION, THE DUCTAL EPITHELIUM OF THE EXOCRINE GLAND WITH A CYTOLYTIC VIRUS TO DESTROY LESS THAN ALL OF THE DUCTAL EPITHELIUM SO AS TO INHIBIT FORMATION OF** CANCER **OF DUCTAL EPITHELIAL ORIGIN**
Inventor: Sukumar, Saraswati Vaidyanathan, Columbia, MD
Assignee: John Hopkins University School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Priebe, Scott D. (Art Unit: 163)
Assistant Examiner: Nguyen, Dave Trong
Law Firm: Leydig, Voit & Mayer, Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6153184	A	20001128	US 9893145	19980608
Division	US 5763415	A		US 96692001	19960802

Fulltext Word Count: 6120

- end of record -

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Display 9/3/22 (Item 22 from file: 654)
DIALOG(R)File 654:US Pat.Full.

4281678
Derwent Accession: 2000-194851
Utility
C/ **Use of an inhibitor of the protein tyrosine kinase pathway in the treatment of choroidal neovascularization**
Inventor: de Juan, Jr., Eugene, Phoenix, MD
Assignee: John Hopkins University, School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Fay, Zohreh (Art Unit: 164)
Law Firm: Leydig, Voit & Mayer, Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 6028099	A	20000222	US 9841601	19980313

Fulltext Word Count: 7625

- end of record -

?
Display 9/3/23 (Item 23 from file: 654)
DIALOG(R)File 654:US Pat.Full.

4229476
Derwent Accession: 1999-551197
Utility
C/ **Use of a protein tyrosine kinase pathway inhibitor in the treatment of retinal ischmemia or ocular inflammation**
; **PROPHYLACTIC AND THERAPEUTIC TREATMENT OF EYE DISORDERS**
Inventor: de Juan, Jr., Eugene, Phoenix, MD
Assignee: Johns Hopkins University, School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Azupuru, Carlos A. (Art Unit: 165)
Law Firm: Leydig, Voit & Mayer, Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 5980929	A	19991109	US 9842440	19980313

Fulltext Word Count: 8822

- end of record -

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Display 9/3/24 (Item 24 from file: 654)
DIALOG(R)File 654:US Pat.Full.

4163809
Derwent Accession: 1999-394644
Utility
REEXAMINED, REEXAMINATION REQUESTED **See File 123 for amended claim
C/ **Use of a protein tyrosine kinase pathway inhibitor in the treatment of diabetic retinopathy**
; **IS PREFERABLY** GENISTEIN **OR AN ANALOGUE OR** PRODRUG **THEREOF**
Inventor: de Juan, Jr., Eugene, Phoenix, MD
Assignee: Johns Hopkins University, School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Weddington, Kevin E. (Art Unit: 164)
Law Firm: Leydig, Voit & Mayer, Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 5919813	A	19990706	US 9841931	19980313

Fulltext Word Count: 6815

- end of record -

?

Display 9/3/25 (Item 25 from file: 654)
DIALOG(R)File 654:US Pat.Full.

3992768
Derwent Accession: 1997-154039

Utility
C/ **Destruction of the epithelium of an exocrine gland in the prophylactic and therapeutic treatment of** cancer
Inventor: Sukumar, Saraswati Vaidyanathan, Columbia, MD
Assignee: John Hopkins University School of Medicine 02), Baltimore, MD
Johns Hopkins University (Code: 39884)
Examiner: Low, Christopher S. F. (Art Unit: 184)
Assistant Examiner: Nguyen, Dave T.
Law Firm: Leydig, Voit & Mayer, Ltd.

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 5763415	A	19980609	US 96692001	19960802
Provisional				US 60-28929	19950803

Fulltext Word Count: 5427

- end of record -

?
Display 9/3/26 (Item 1 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
(c) 2005 WIPO/Univentio. All rts. reserv.

01187183 **Image available**
TRANSDUCIBLE DNA-BINDING PROTEINS
PROTEINES DE LIAISON A L'ADN DE TRANSDUCTION
Patent Applicant/Assignee:
TOOLGEN INC, Daedeok Biocommunity, 461-6, Jeonmin-dong, Yuseong-gu, Daejeon 305-390, KR, KR (Residence), KR (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
KIM Jin-Soo, #202, Jeonmin-dong, 299-8, Yuseong-gu, Daejeon 305-390, KR, KR (Residence), KR (Nationality), (Designated only for: US)
SHIN Hyun-Chul, Expo Apt. 407-1704, Jeonmin-dong, Yuseong-gu, Daejeon 305-390, KR, KR (Residence), KR (Nationality), (Designated only for: US)
KWON Heung-Sun, Sangroksu Apt. 103-1508, Mannyun-dong, Seo-gu, Daejeon 302-781, KR, KR (Residence), KR (Nationality), (Designated only for: US)
Legal Representative:
JANG Seongku (et al) (agent), 19th Fl., KEC Building,, #275-7, Yangjae-dong,, Seocho-ku, Seoul 137-130, KR,
Patent and Priority Information (Country, Number, Date):
Patent: WO 2004108883 A2 20041216 (WO 04108883)
Application: WO 2004KR1385 20040610 (PCT/WO KR04001385)
Priority Application: US 2003477459 20030610
Designated States:
(All protection types applied unless otherwise stated - for applications 2004+)
AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG

(AP) BW GH GM KE LS MW MZ NA SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 28475

- end of record -

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Display 9/3/27 - (Item 2 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

01118708

AMINATED ISOFLAVONOID DERIVATIVES AND USES THEREOF
DERIVES D'ISOFLAVONOIDES AMINES ET LEURS UTILISATIONS

Patent Applicant/Assignee:
NOVOGEN RESEARCH PTY LTD, 140 Wicks Road, North Ryde, New South Wales 2113, AU, AU (Residence), AU (Nationality), (For all designated states except: US)

Patent Applicant/Inventor:
KELLY Graham Edmund, 47 Coolawin Street, Northbridge, New South Wales 2063, AU, AU (Residence), AU (Nationality), (Designated only for: US)
HEATON Andrew, 2/46-48 Abbotsford Parade, Abbotsford, New South Wales 2046, AU, AU (Residence), AU (Nationality), (Designated only for: US)
FARAGALLA Jane, 17 Manning Place, Seven Hills, New South Wales 2147, AU, AU (Residence), AU (Nationality), (Designated only for: US)
BREMNER John, 38 The Parkway, Balgownie, New South Wales 2519, AU, AU (Residence), AU (Nationality), (Designated only for: US)

Legal Representative:
HEISEY Ross Mitchell (et al) (agent), Davies Collison Cave, Level 10, 10 Barrack Street, Sydney, New South Wales 2000, AU,

Patent and Priority Information (Country, Number, Date):
Patent: WO 200439793 A1 20040513 (WO 0439793)
Application: WO 2003AU1446 20031103 (PCT/WO AU03001446)
Priority Application: AU 2002952453 20021101

Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English
Filing Language: English
Fulltext Word Count: 12211

- end of record -

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Display 9/3/28 (Item 3 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

01110068 **Image available**
HUMAN SARCOMA-ASSOCIATED ANTIGENS
ANTIGENES ASSOCIES AU SARCOME HUMAIN
Patent Applicant/Assignee:
LUDWIG INSTITUTE FOR **CANCER** RESEARCH, 605 Third Avenue, New York, NY 10158, US, US (Residence), CH (Nationality), (For all designated states except: US
Patent Applicant/Inventor:
SCANLAN Matthew J, Ludwig Institute for Cancer Research, 605 Third Avenue, New York, NY 10158, US, US (Residence), US (Nationality), (Designated only for: US)
LEE Sang-Yull, Ludwig Institute for Cancer Research, 605 Third Avenue, New York, NY 10158, US, US (Residence), US (Nationality), (Designated only for: US)
OLD Lloyd J, Ludwig Institute for Cancer Research, 605 Third Avenue, New York, NY 10158, US, US (Residence), US (Nationality), (Designated only for: US)
Legal Representative:
VAN AMSTERDAM John R (agent), Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210, US,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200431354 A2 20040415 (WO 0431354)
Application: WO 2003US30870 20030930 (PCT/WO US03030870)
Priority Application: US 2002260708 20020930
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 43612

- end of record -

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Display 9/3/29 (Item 4 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

01066404 **Image available**
POLYDIAZENIUMDIOLATED CYCLIC POLYAMINES WITH POLYPHASIC NITRIC OXIDE RELEASE AND RELATED COMPOUNDS, COMPOSITIONS COMPRISING SAME AND METHODS OF USING SAME
POLYAMINES CYCLIQUES POLYDIAZENIUMDIOLEES LIBERANT DE L'ACIDE NITRIQUE POLYPHASIQUE, COMPOSES ET COMPOSITIONS LES COMPRENANT, ET PROCEDES D'UTILISATION ASSOCIES
Patent Applicant/Assignee:
THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by the secretary DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852, US

, US (Residence), US (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
WATERHOUSE David J, 908 Gatepost Lane #1E, Frederick, MD 21701, US, US (Residence), US (Nationality), (Designated only for: US)
KAPUR Preeya, 8577 Indian Springs Road, Frederick, MD 21702, US, US (Residence), US (Nationality), (Designated only for: US)
KEEFER Larry K, 7016 River Road, Bethesda, MD 20817, US, US (Residence), US (Nationality), (Designated only for: US)
HRABIE Joseph A, 630 Grant Place, Frederick, MD 21702, US, US (Residence), US (Nationality), (Designated only for: US)
Legal Representative:
LOWE Jeremy C (et al) (agent), Leydig, Voit & Mayer, Ltd., Two Prudential Plaza, Suite 4900, 180 North Stetson, Chicago, IL 60601-6780, US,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200395398 A2-A3 20031120 (WO 0395398)
Application: WO 2003US14180 20030507 (PCT/WO US03014180)
Priority Application: US 2002378495 20020507
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 18584

- end of record -

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Display 9/3/30 (Item 5 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

01065024
METHODS OF TREATMENT OF GLAUCOMA AND OTHER CONDITIONS MEDIATED BY NOS-2 EXPRESSION VIA INHIBITION OF THE EGFR PATHWAY
METHODES DE TRAITEMENT DU GLAUCOME ET D'AUTRES ETATS INDUITS PAR L'EXPRESSION DE NOS-2 PAR INHIBITION DE LA VOIE EGFR
Patent Applicant/Assignee:
WASHINGTON UNIVERSITY, One Brookings Drive, St. Louis, MO 63130, US, US (Residence), US (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
LIU Bin, 5626 Oleatha, St. Louis, MO 63139, US, US (Residence), CN (Nationality), (Designated only for: US)
NEUFELD Arthur H, 110 West Pine Place, St. Louis, MO 63108, US, US (Residence), US (Nationality), (Designated only for: US)
Legal Representative:
BLOSSER Harley G (agent), Sonnenschein, Nath & Rosenthal, Attention: IP Department-St. Louis Office, P.O. Box #061080, Wacker Drive Station-Sears Tower, Chicago, IL 60606-1080, US,

Patent and Priority Information (Country, Number, Date):
  Patent: WO 200392693 A1 20031113 (WO 0392693)
  Application: WO 2003US14484 20030506 (PCT/WO US0314484)
  Priority Application: US 2002378254 20020506
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
  AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ
  EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
  LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG
  SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
  (EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE
  SI SK TR
  (OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
  (AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
  (EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 13416

- end of record -

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Display 9/3/31 (Item 6 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

01064860
TUMOR SUPPRESSOR GENE POLYPEPTIDES AND RELATED NUCLEIC ACIDS, HOST CELLS, COMPOSITIONS, AND METHODS OF USE IN INHIBITION OF CELL GROWTH, MODULATION OF GENE EXPRESSION, AND ENHANCEMENT OF IMMUNE-RESPONSE INDUCING EFFECT OF A VACCINE
POLYPEPTIDES DE GENE SUPPRESSEUR DE TUMEUR, ACIDES NUCLEIQUES, CELLULES HOTES ET COMPOSITIONS ASSOCIEES, METHODES D'UTILISATION PERMETTANT D'INHIBER LA CROISSANCE CELLULAIRE, MODULATION DE L'EXPRESSION GENIQUE ET AMELIORATION D'UNE REPONSE IMMUNITAIRE INDUISANT UN EFFET DE VACCIN
Patent Applicant/Assignee:
  GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY DEPARTMENT OF HEALTH AND HUMAN SERVICES, National Institute of Health, Office of Technology Transfer, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852, US, US (Residence), US (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
  SIMMONS Denise Perry, 15301-B Gable Ridge Ct., Rockville, MD 20850, US, US (Residence), US (Nationality), (Designated only for: US)
Legal Representative:
  LARCHER Carol (et al) (agent), Leydig, Voit & Mayer, Ltd., Suite 4900, Two Prudential Plaza, 180 North Stetson, Chicago, IL 60601-6780, US,
Patent and Priority Information (Country, Number, Date):
  Patent: WO 200392593 A2 20031113 (WO 0392593)
  Application: WO 2003US13287 20030501 (PCT/WO US0313287)
  Priority Application: US 2002377827 20020503
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
  AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ
  EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR

LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG
SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE
SI SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 16304

- end of record -

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Display 9/3/32 (Item 7 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

01043835
DNA-BINDING POLYAMIDE DRUG CONJUGATES
CONJUGUES MEDICAMENTEUX DE POLYAMIDE DE LIAISON A L'ADN
Patent Applicant/Assignee:
THE GOVERNMENT OF THE UNITED STATES OF AMERICA representated by THE SECRETARY DEPARMENT OF HEALTH AND HUMAN SERVICES, National Institutes of Health, Office of Technology Transfer, 6011 Executive Boulevard, Suite 235, Rockville, MD 20852, US, US (Residence), US (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
SZEKELY Zoltan, 6 Bannister Ct., Gaithersburg, MD 20879, US, US (Residence), HU (Nationality), (Designated only for: US)
HARIPRAKASHA Humcha Krishnamurthy, 1418G Taney Avenue, #301, Frederick, MD 21702, US, US (Residence), IN (Nationality), (Designated only for: US)
CHOLODY Marek W, 902 Halleck Dr., Frederick, MD 21702, US, US (Residence), US (Nationality), (Designated only for: US)
MICHEJDA Christopher J, 13814 Hidden Glen Lane, North Potomac, MD 20878, US, US (Residence), US (Nationality), (Designated only for: US)
Legal Representative:
LARCHER Carol (et al) (agent), Leydig, Voit & Mayer, Ltd., Two Prudential Plaza, Suite 4900, 180 North Steton, Chicago, IL 60601-6780, US,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200372058 A2-A3 20030904 (WO 0372058)
Application: WO 2003US6006 20030227 (PCT/WO US03006006)
Priority Application: US 2002361050 20020227; US 2002370168 20020405
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ
EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG
SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE SI
SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English

Filing Language: English
Fulltext Word Count: 11990

- end of record -

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Display 9/3/33 (Item 8 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

01005317 **Image available**

PSMA ANTIBODIES AND PROTEIN MULTIMERS
ANTICORPS ET MULTIMERES DE PROTEINES PSMA

Patent Applicant/Assignee:
PSMA DEVELOPMENT COMPANY L L C, Progenics Pharmaceuticals, 777 Old Saw Mill River Road, Tarrytown, New York 10591, US, US (Residence), US (Nationality), (For all designated states except: US)

Patent Applicant/Inventor:
MADDON Paul J, 191 Fox Meadow Road, Scarsdale, NY 10583, US, US (Residence), US (Nationality), (Designated only for: US)
DONOVAN Gerald P, 430 East 63rd Street, Apartment 5L, New York, NY 10021, US, US (Residence), US (Nationality), (Designated only for: US)
OLSON William C, 21 Fawn Court, Ossining, NY 10562, US, US (Residence), US (Nationality), (Designated only for: US)
SCHULKE Norbert, 101 Ridge Road, New City, NY 10956, US, US (Residence), US (Nationality), (Designated only for: US)
GARDNER Jason, 24 Bramble Brook Road, Ardsley, NY 10502, US, US (Residence), US (Nationality), (Designated only for: US)
MA Dangshe, 49 Glenwood Road, Millwood, NY 10546, US, US (Residence), US (Nationality), (Designated only for: US)

Legal Representative:
VAN AMSTERDAM John R (agent), Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210, US,

Patent and Priority Information (Country, Number, Date):
Patent: WO 200334903 A2-A3 20030501 (WO 0334903)
Application: WO 2002US33944 20021023 (PCT/WO US02033944)
Priority Application: US 2001335215 20011023; US 2002362747 20020307; US 2002412618 20020920

Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM

Publication Language: English
Filing Language: English
Fulltext Word Count: 48651

- end of record -

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Display 9/3/34 (Item 9 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

00942163
TREATMENT OF RESTENOSIS
TRAITEMENT DE LA RESTENOSE
Patent Applicant/Assignee:
NOVOGEN RESEARCH PTY LTD, 140 Wicks Road, North Ryde, New South Wales 2113, AU, AU (Residence), AU (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
HUSBAND Alan, 2/18 West Crescent Street, McMahon's Point, New South Wales 2060, AU, AU (Residence), AU (Nationality), (Designated only for: US)
KELLY Graham Edmund, 47 Coolawin Street, Northbridge, New South Wales 2063, AU, AU (Residence), AU (Nationality), (Designated only for: US)
Legal Representative:
HEISEY Ross Mitchell (et al) (agent), DAVIES COLLISON CAVE, Level 10, 10 Barrack Street, Sydney, NSW 2000, AU,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200274307 A1 20020926 (WO 0274307)
Application: WO 2002AU288 20020315 (PCT/WO AU0200288)
Priority Application: AU 20013770 20010316; AU 20015926 20010626
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ
EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 20450

- end of record -

?

Display 9/3/35 (Item 10 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00926501
MEANS AND METHODS FOR TREATMENT EVALUATION
MOYENS ET PROCEDES D'EVALUATION D'UN TRAITEMENT
Patent Applicant/Assignee:
PRIMAGEN HOLDING B V, Meibergdreef 59, NL-1105 BA Amsterdam, NL, NL (Residence), NL (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
VAN DER KUYL Antoinette Cornelia, Van Collenstraat 26, NL-1231 VS Loosdrecht, NL, NL (Residence), NL (Nationality), (Designated only for: US)
CORNELISSEN Marion, Wipmolen 21, NL-3642 AC Loosdrecht, NL, NL (Residence), NL (Nationality), (Designated only for: US)
Legal Representative:

PRINS A W (agent), c/o Vereenigde, Nieuwe Parklaan 97, NL-2587 BN The Hague, NL,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200259558 A2-A3 20020801 (WO 0259558)
Application: WO 2002NL51 20020123 (PCT/WO NL0200051)
Priority Application: EP 2001200228 20010123; EP 2001203703 20010928; US 2001325722 20010928
Parent Application/Grant:
Related by Addition to: CU Not furnished (ICA)
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT (utility model) AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU (inventor's certificate) CZ (utility model) CZ DE (utility model) DE DK (utility model) DK DM DZ EC EE (utility model) EE ES FI (utility model) FI GB GD GE GH GM HR (consensual patent) HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK (utility model) SK SL TJ TM TN TR TT (utility certificate) TZ UA UG (utility certificate) US UZ VN YU ZA ZM ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 14107

- end of record -

?

Display 9/3/36 (Item 11 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00755880
THE USE OF A PROTEIN TYROSINE KINASE PATHWAY INHIBITOR IN THE TREATMENT OF OCULAR DISORDERS
UTILISATION D'UN INHIBITEUR DE TRAJET DE PROTEINE TYROSINE KINASE DANS LE TRAITEMENT DES TROUBLES OCULAIRES
Patent Applicant/Assignee:
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, Suite 906, 111 Market Place, Baltimore, MD 21202, US, US (Residence), US (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
DE JUAN Eugene Jr, 13721 Poplar Hill Road, Phoenix, MD 21131, US, US (Residence), US (Nationality), (Designated only for: US)
Legal Representative:
LARCHER Carol (et al) (agent), Leydig, Voit & Mayer, Ltd., Suite 4900, Two Prudential Plaza, 180 North Stetson, Chicago, IL 60601-6780, US,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200067738 A2-A3 20001116 (WO 0067738)
Application: WO 2000US12339 20000505 (PCT/WO US0012339)
Priority Application: US 99133112 19990507; US 99350440 19990709
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES

FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU
LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT
TZ UA UG US UZ VN YU ZA ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
(OA) BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
(AP) GH GM KE LS MW SD SL SZ TZ UG ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 10026

- end of record -

?

Display 9/3/37 (Item 12 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
(c) 2005 WIPO/Univentio. All rts. reserv.

00514568
THE USE OF A PROTEIN TYROSINE INHIBITOR SUCH AS GENISTEIN IN THE TREATMENT OF DIABETIC RETINOPATHY OR OCULAR INFLAMMATION
TRAITEMENT DE LA RETINOPATHIE DIABETIQUE OU DES INFLAMMATIONS OCULAIRES AU MOYEN D'UN INHIBITEUR DES TYROSINE-KINASES TEL QUE LA GENISTEINE
Patent Applicant/Assignee:
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE,
DE JUAN Eugene,
Inventor(s):
DE JUAN Eugene,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9945920 A2 19990916
Application: WO 99US5477 19990312 (PCT/WO US9905477)
Priority Application: US 9841931 19980313; US 9842440 19980313
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH
GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN
MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU
ZW GH GM KE LS MW SD SL SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML
MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 7967

- end of record -

?

Display 9/3/38 (Item 13 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
(c) 2005 WIPO/Univentio. All rts. reserv.

00435422 **Image available**
NOVEL COMPOUNDS USEFUL AS THERAPEUTIC AGENTS AND ASSAY REAGENTS
NOUVEAUX COMPOSES UTILES COMME AGENTS THERAPEUTIQUES ET COMME REACTIFS D'ANALYSE
Patent Applicant/Assignee:
RILEY Patrick Anthony,

PHOTIOU Andrew,
KHAN Tariq Hussain,
OSBORN Helen Mary Isted,
Inventor(s):
RILEY Patrick Anthony,
PHOTIOU Andrew,
KHAN Tariq Hussain,
OSBORN Helen Mary Isted,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9825886 A1 19980618
Application: WO 97GB3433 19971212 (PCT/WO GB9703433)
Priority Application: GB 9625895 19961213
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU
ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ
PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE
LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB
GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
Publication Language: English
Fulltext Word Count: 5902

- end of record -

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Display 9/3/39 (Item 14 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
(c) 2005 WIPO/Univentio. All rts. reserv.

00365572 **Image available**
DELIVERY OF AN AGENT TO THE DUCTAL EPITHELIUM IN THE PROPHYLACTIC AND THERAPEUTIC TREATMENT OF CANCER
DESTRUCTION DE L'EPITHELIUM D'UNE GLANDE EXOCRINE DANS LE TRAITEMENT PROPHILACTIQUE ET THERAPEUTIQUE DU CANCER
Patent Applicant/Assignee:
THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE,
Inventor(s):
SUKUMAR Saraswati Vaidyanathan,
Patent and Priority Information (Country, Number, Date):
Patent: WO 9705898 A1 19970220
Application: WO 96US12837 19960802 (PCT/WO US9612837)
Priority Application: US 95510623 19950803
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AU CA JP AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
Publication Language: English
Fulltext Word Count: 6969

- end of record -

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Display 9/3/40 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
(c) 2005 European Patent Office. All rts. reserv.

01560186
Means and methods for treatment evaluation
Mittel und Methoden fur die Abschatzung einer Behandlung
Moyens et methodes pour l'evaluation d'un traitement
PATENT ASSIGNEE:
PrimaGen Holding B.V., (3353291), Meibergdreef 59, 1105 BA Amsterdam, (NL), (Applicant designated States: all)
INVENTOR:
van der Kuyl, Antoinette C., Van Collenstraat 26, 1231 VS Loosdrecht, (NL)
Cornelissen, Marion, Wipmolen 21, 3642 AC Mijdrecht, (NL)
LEGAL REPRESENTATIVE:
Prins, Adrianus Willem et al (20903), Vereenigde, Nieuwe Parklaan 97, 2587 BN Den Haag, (NL)
PATENT (CC, No, Kind, Date): EP 1298221 A1 030402 (Basic)
APPLICATION (CC, No, Date): EP 2001203703 010928;
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE; TR
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12Q-001/68
ABSTRACT WORD COUNT: 139
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200314	1119
SPEC A	(English)	200314	9430
Total word count - document A			10549
Total word count - document B			0
Total word count - documents A + B			10549

- end of record -

?

Display 9/3/41 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01439401
Means and methods for treatment evaluation
Mittel und Methoden fur die Abschatzung einer Behandlung
Moyens et methodes pour l'evaluation d'un traitement
PATENT ASSIGNEE:
Amsterdam Support Diagnostics B.V., (2376391), Twin-2, Building R-South, Meibergdreef 59, 1105 BA Amsterdam, (NL), (Applicant designated States: all)
INVENTOR:
van der Kuyl, Antoinette Cornelia, Van Collenstraat 26, 1231 VS Loosdrecht, (NL)
Cornelissen, Marion, Wipmolen 21, 3642 AC Mijdrecht, (NL)
LEGAL REPRESENTATIVE:
Prins, Adrianus Willem et al (20903), Vereenigde, Nieuwe Parklaan 97, 2587 BN Den Haag, (NL)
PATENT (CC, No, Kind, Date): EP 1225233 A2 020724 (Basic)
EP 1225233 A3 030108

APPLICATION (CC, No, Date): EP 2002075264 020123;
PRIORITY (CC, No, Date): EP 2001200228 010123; EP 2001203703 010928; US 325722 P 010928
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE; TR
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12Q-001/68
ABSTRACT WORD COUNT: 139
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200230	1121
SPEC A	(English)	200230	9705
Total word count - document A			10826
Total word count - document B			0
Total word count - documents A + B			10826

- end of record -

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Display 9/3/42 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

10475343 2003-0219772 2003-0066297
C/MEANS AND METHODS FOR TREATMENT EVALUATION; EVALUATING EFFECTIVENESS OF CANCER TREATMENT; DRUG SCREENING
Inventors: Cornelissen Marion (NL); Kuyl Antoinette Cornelia van der (NL)
Assignee: Unassigned Or Assigned To Individual
Assignee Code: 68000

	Publication Number	Kind	Date	Application Number	Date
	US 20030219772	A1	20031127	US 2002310677	20021205
Cont.-in-part of:				US 200255728	20020123
Priority Applic:				US 2002310677	20021205
				US 200255728	20020123
Provisional Applic:				US 60-325722	20010928

- end of record -

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Display 9/3/43 (Item 1 from file: 484)
DIALOG(R)File 484:Periodical Abs Plustext

05030542 SUPPLIER NUMBER: 71514165 (USE FORMAT 7 OR 9 FOR FULLTEXT)
Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements
Setchell, Kenneth D R; Brown, Nadine M; Desai, Pankaj; Zimmer-Nechemias, Linda; Et al
Journal of Nutrition (IJNU), v131 n4S, pS1362-S1375, p.14
Apr 2001

ISSN: 0022-3166 JOURNAL CODE: IJNU
DOCUMENT TYPE: Feature
LANGUAGE: English RECORD TYPE: Fulltext; Abstract
WORD COUNT: 10845

- end of record -

?

Display 9/3/44 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0320882 DBR Accession No.: 2003-22022 PATENT
Determining whether a treatment is effective in changing a status of a certain set of target cells in an individual comprises determining whether the sample comprises an expression product of at least one marker gene - keratin-14, TIE-1, Salioadhesin and Siglec-1 gene expression profiling for use in drug screening and cancer **therapy**
AUTHOR: VAN DER KUYL A C; CORNELISSEN M
PATENT ASSIGNEE: PRIMAGEN HOLDING BV 2003
PATENT NUMBER: EP 1298221 PATENT DATE: 20030402 WPI ACCESSION NO.: 2003-589342 (200356)
PRIORITY APPLIC. NO.: EP 2001203703 APPLIC. DATE: 20010928
NATIONAL APPLIC. NO.: EP 2001203703 APPLIC. DATE: 20010928
LANGUAGE: English

- end of record -

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Display 9/3/45 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0300565 DBR Accession No.: 2003-02349 PATENT
Determining presence of a tumor cell or angiogenesis, and the effectiveness of treatment, by detecting the presence of marker genes is useful to detect and monitor treatment of Karposi's Sarcoma - tumor marker gene expression and quantification for disease diagnosis and therapy
AUTHOR: VAN DER KUYL A C; CORNELISSEN M
PATENT ASSIGNEE: AMSTERDAM SUPPORT DIAGNOSTICS BV 2002
PATENT NUMBER: EP 1225233 PATENT DATE: 20020724 WPI ACCESSION NO.: 2002-668396 (200272)
PRIORITY APPLIC. NO.: US 325722 APPLIC. DATE: 20010928
NATIONAL APPLIC. NO.: EP 200275264 APPLIC. DATE: 20020123
LANGUAGE: English

- end of record -

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Display 9/3/46 (Item 1 from file: 452)
DIALOG(R)File 452:Drug Data Report

00284427 (Structure Image Available)
GENERIC NAME Genistein-7-phosphate
CHEM NAME: Phosphoric acid 5-hydroxy-3-(4-hydroxyphenyl)-4-oxo-4H-1-benzopyran- 7-yl monoester

FORMULA: C15H11O8P
DEVEL. PHASE: Biological Testing
ORIGINATOR: Vyrex
CLASS: 50050 (Treatment of Osteoporosis)
75000 (Oncolytic Drugs)
RELATED ENTRY: 122175 (non-specific)
PREV. PUB. IN: Drug Data Report, Vol. 22, No. 2, p. 187, 2000

- end of record -
?

Display 9/3/47 (Item 1 from file: 759)
DIALOG(R)File 759:Business Insights

00112622

OVERVIEW: 1.11 ADJUVANTS

Main Title: THE NEW **CANCER** THERAPEUTICS MARKET
Pub. Date: April 04, 2003
Source: DATAMONITOR
Telephone: +44 20 7675 7000
Word Count: 1147 (1 pp.)
Language: English

Country: WORLD
Industry: HEALTH CARE

- end of record -
?

Display 9/3/48 (Item 1 from file: 761)
DIALOG(R)File 761:Datamonitor Market Res.

00227766

AN ANALYSIS OF CURRENT AND EMERGING MARKETS: Adjuvants

Main Title: NEW **CANCER** THERAPEUTICS
Pub. Date: November 30, 2002
Source: DATAMONITOR
Telephone: +44 20 7675 7000
Word Count: 1147 (1 pp.)
Language: English

Country: WORLD
Industry: HEALTH CARE

- end of record -
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Set	Items	Description
S1	1007	(ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES

```
             OR DIHYDROISOFLAVONE OR DAIDZEIN OR GENISTEIN OR GLYCITEIN) -
            AND (PRODRUG OR PRODRUGS OR PRO()DRUG OR PRO()DRUGS)
S2           3   S1 AND DT=REVIEW
S3           3   RD (unique items)
S4        4867   (PRODRUG OR PRODRUGS) AND DT=REVIEW
S5           2   S4 AND (DAIDZEIN OR GENISTEIN OR GLYCITEIN)
S6           2   RD (unique items)
S7          74   (DAIDZEIN OR GENISTEIN OR GLYCITEIN)(10N)(PRODRUG OR PRODR-
             UGS)
S8          66   RD (unique items)
S9          48   S8 AND (CANCER)
? d s9/7/27,38,43
>>>Format 7 is not valid in file 759
>>>Format 7 is not valid in file 761
      Display 9/7/27     (Item 2 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
(c) 2005 WIPO/Univentio. All rts. reserv.

01118708
AMINATED ISOFLAVONOID DERIVATIVES AND USES THEREOF
DERIVES D'ISOFLAVONOIDES AMINES ET LEURS UTILISATIONS
Patent Applicant/Assignee:
  NOVOGEN RESEARCH PTY LTD, 140 Wicks Road, North Ryde, New South Wales
    2113, AU, AU (Residence), AU (Nationality), (For all designated states
    except: US)
Patent Applicant/Inventor:
  KELLY Graham Edmund, 47 Coolawin Street, Northbridge, New South Wales
    2063, AU, AU (Residence), AU (Nationality), (Designated only for: US)
  HEATON Andrew, 2/46-48 Abbotsford Parade, Abbotsford, New South Wales
    2046, AU, AU (Residence), AU (Nationality), (Designated only for: US)
  FARAGALLA Jane, 17 Manning Place, Seven Hills, New South Wales 2147, AU,
    AU (Residence), AU (Nationality), (Designated only for: US)
  BREMNER John, 38 The Parkway, Balgownie, New South Wales 2519, AU, AU
    (Residence), AU (Nationality), (Designated only for: US)
Legal Representative:
  HEISEY Ross Mitchell (et al) (agent), Davies Collison Cave, Level 10, 10
    Barrack Street, Sydney, New South Wales 2000, AU,
Patent and Priority Information (Country, Number, Date):
  Patent:               WO 200439793 A1 20040513 (WO 0439793)
  Application:          WO 2003AU1446 20031103  (PCT/WO AU03001446)
  Priority Application: AU 2002952453 20021101
Designated States:
(Protection type is "patent" unless otherwise stated - for applications
prior to 2004)
  AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM
  DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
  LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU
  SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
  (EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE
  SI SK TR
  (OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
  (AP) BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
  (EA) AM AZ BY KG KZ MD RU TJ TM
Main International Patent Class: C07D-311/68
International Patent Class: A61K-031/352; A61P-035/00
Publication Language: English
Filing Language: English
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Fulltext Word Count: 12211

English Abstract
Aminated isoflavonoid synthesized by aminating the 4-keto group of isoflavanone and isoflavanone ring systems, pharmaceutical compositions containing same and uses thereof as therapeutic agents.

French Abstract
L'invention se rapporte a des derives d'isoflavonoides amines synthetises par amination du groupe 4-carbonyle d'isoflavanones et de systemes cycliques d'isoflavanones, a des compositions pharmaceutiques les contenant, ainsi qu'a leur utilisation en tant qu'agents therapeutiques.

Legal Status (Type, Date, Text)
Publication 20040513 A1 With international search report.
Examination 20040715 Request for preliminary examination prior to end of 19th month from priority date

Claim
Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.
Brief Description of the Figures
Fig. I represents cytotoxicity curves for Cpd. 1 and Cpd. 3 against selected tumor lines
LNCaP, DU145 and NCI-H460 as follows:
Graph A Cpd. 1 / LNCaP
Graph B Cpd. 1 / DUI45
Graph C Cpd. 3 / LNCaP
Graph D Cpd. 3 / NCI-H460
20 Fig. 2 represents the inhibition of testosteron'e induced LNCaP proliferation by Cpd. 1 (Graph A), and Cpd. 2 and Cpd. 3 (Graph B). Fig. 3 represents an inhibition profile of testosterone-induced LNCaP proliferation for Cpd. 1, Cpd. 2 and Cpd. 3. Fig. 4 represents the inhibition of COS (PGE 3) and thromboxane synthase (TBXZ) activity by Cpd. 1, Cpd. 2 and Cpd. 3
Fig. 5 represents the 1H n.m.r. spectrum (d6-acetone) of Cpd. 1. Fig. 6 represents the 1H n.m.r. spectrum (d3-acetonitrile) of Cpd. 2.
1
Fig. 7 represents the 1H n.m.r. spectrum (d3-acetonitrile) of Cpd. 3.
Detailed Description of the Invention
The aminated compounds of the present invention are based on isoflavone compounds kd derivatives thereof. The term "isoflavone" as used herein is to be taken broadly to include ring-fused benzopyran molecules having a pendent phenyl group from the pyran ring based on a 1,2-diphenylpropane system. Thus, the classes of compounds generally referred to as 1 0 isoflavones, isoflavenes, isoflavans, isoflavanones, isoflavanols and the like are generically referred to herein as isoflavones, isoflavone derivatives or isoflavonoid molecules, compounds or derivatives. The term "alkyl" is taken to include straight chain, branched chain and cyclic (in the case 1 5 of 5 carbons or greater) saturated alkyl groups of 1 to 10 carbon atoms, preferably from 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, tertiary butyl, pentyl, cyclopentyl, and the like. The alkyl group is more preferably methyl, ethyl, propyl or isopropyl. The alkyl group may optionally be substituted

by one or more of fluorine, chlorine, bromine, iodine, carboxyl, Cl-C4-alkoxycarbonyl, Cl-C4-alkylarninocarbonyl, di-(CI-C4-alkyl)-amino-carbonyl, hydroxyl, Cl-C4-alkoxy, formyloxy, Cl-C4alkyl-carbonyloxy, Cl-C4-alkylthio, C3-C6-cycloalkyl or phenyl. The term "alkenyl" is taken to include straight chain, branched chain and cyclic (in the case of 5 carbons or greater) hydrocarbons of 2 to 1 0 carbon atoms, preferably 2 to 6 carbon atoms, with at lease one double bond such as ethenyl, 1 -propenyl, 2-propenyl, 1 -butenyl, 2-butenyl, 2-methyl-l-peopenyl, 2-methyl propenyl, and the like. The alkenyl group is more preferably ethenyl, 1-propenyl or 2-propenyl. The alkenyl groups may optionally be substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, CI-C4alkoxycarbonyl, Q-C4-alkylamino-carbonyl, di-(Cl-C4-alkyl)-ainino-carbonyl, hydroxyl, Cl-C4-alkoxy, formyloxy, Cl-C4-alkyl-carbonyloxy, Cl-C4-alkylthio, C3-C6-cYClOalkyl or phenyl. -10 The tenn "alkynyl" is taken to include both straight chain and branched chain hydrocarbons of 2 to 10 carbon atoms, preferably 2 to 6 carbon atoms, with at least one triple bond such as ethynyl, 1 -propynyl, 2-propynyl, 1 -butynyl, 2-butynyl, and the like. The alkynyl group is more preferably ethynyl, 1 -propynyl or 2-propynyl. The alkynyl group may optionally be substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, Cl-C4-alkoxycarbonyl, CI-C4-alkylamino-carbonyl, di-(Cj-C4-alkyl)-aminocarbonyl, hydroxyl, CI-C4-alkoxy, formyloxy, Cl-C4-alkyl-carbonyloxy, Cl-C4-alkylthio, C3-C6-cycloalkyl or phenyl.
0
The term "aryl" is taken to include phenyl, biphenyl and naphthyl and may be optionally substituted by one or more CI-C4-alkyl, hydroxy, CI-C4-alkoxy, carbonyl, Cl-C4alkoxycarbonyl, Cl-C4-alkylcarbonyloxy, nitro or halo. The term "heteroaryl" is taken to include five-mernbered and six-membered rings which include at least one oxygen, sulfur or nitrogen in the ring, which rings may be optionally fused to other aryl or heteroaryl rings including but not limited to faryl, pyridyl, pyrimidyl, thienyl, imidazolyl, tetrazolyl, pyrazinyl, benzofuranyl, benzothiophenyl, quinolyl, isopuinolyl, purinyl, morpholinyl,'oxazolyl, thiazolyl, pyrrolyl, xanthinyl, purine, thymine, cytosine, uracil, and isoxazolyl. The heteroaromatic group can be optionally substituted by one or more of fluorine, chlorine, bromine, iodine, carboxyl, nitro, Cl-C4-alkoxycarbonyl, Q-C4-alkylarnino-carbonyl, di-(CI-C4-alkyl)-amino-carbonyl, hydrOXYl, CI-C4-alkoxy, formyloxy, Cl-C4-alkyl-carbonyloxy, Cl-C4-alkylthio, C3-C6-cycloalkyl or phenyl. The heteroaromatic can be partially or totally hydrogenated as desired. The term "halo" is taken to include fluoro, chloro, bromo and iodo, preferably fluoro and chloro, more preferably fluoro. Reference to for example "haloalkyl" will include monohalogenated, dihalogenated and up to perhalogenated alkyl groups. Preferred haloalkyl groups are trifluoromethyl and pentafluoroethyl. Optionally substituted groups are those groups where one or more hydrogens have independently been replaced by hydroxy, alkoxy, acyl, thio, aklyl thio, cyano, nitro, amino, alkylamino, dialkylarnino, halo or carboxy. 5 The present inventors have discovered a new class of molecules based on aminated isoflavonoid derivatives. The invention relates to the substitution of the 4-keto group of isoflavone and isoflavanone compounds by nitrogen-based moieties. In particular the aminated isoflavone derivatives relate to imines, hydrazones, semicarbazones, azines and oximes as depicted by the general formulae (II)-(VIII):

R8 R8
0 R, R7 0 R1
R2 R2

R
R5 R4 R,5 es, R4
R13 R3 / N
R3
(11) R14 R15 M
R8 R8
R7 0 R, R7 0 R1
R2 R2
R R
R5 SI R4 R5 R4
R13N R3 N R3
0 (IV) R16 R17 M
R14 R15
1 5
- 12
R8 R8
R7 0 RI R7 0 RI
R2 R2
R R
R5 CeN R K5 NH R
0 R R13 R3 4
1 3
R13 (VI) (V19)
R8
R7 0 RI
R2
R
R5 R4
R4 R3 R3
N R5
R6
RI 0 R7
R8 (VHD
wherein
R1, R2, R3, R4, R5, R6, R7 and R8 are independently hydrogen, hydroxy, OR9, OC(O)Rq, OS(O)Rg, alkyl, aryl, arylalkyl, thio, alkylthio, bromo, chloro or fluoro,
R9 is alkyl, fluoroalkyl or arylalkyl,
R13, R14 and R15 are independently hydrogen, amino, cyano, thio, nitro, or optionally substituted alkyl, haloalkyl, acyl, aryl, arylalkyl. or alkylaryl, or the substituents R14 and R15 together with the nitrogen atom to which they are attached form an optionally substituted cyclic heteroalkyl. or heteroaromatic structure,
R16 and R17 are independently hydrogen, amino, cyano, thio, nitro or optionally substituted alkyl, haloalkyl, acyl, aryl, arylalkyl. or alkylaryl, or the substituents R16 and R17 taken together with the carbon atom to which they are attached fonn an optionally substituted isoflavonoid ring system, and
the drawing represents either a single bond or a double bond;
more preferably they have the following substituents wherein
RI is hydrogen,
R2, R3, Rs, Rr, and R8 are independently hydrogen, hydroxy, OR9, OC(O)Rq, alkyl, aryl or
arylalkyl,
R4 and R7 are independently hydroxy, OR9 or OC(O)Rq,
R9 is methyl, ethyl, propyl, isopropyl or trifluoromethyl, and
R13, R14 and R15 are independently hydrogen, methyl, ethyl, propyl,

isopropyl, trifluoromethyl or optionally substituted phenyl, naphthyl or benzyl, or the substituents R14 and R15 together with the nitrogen atom to which they are attached form an optionally
substituted cyclic heteroalkyl or heteroaromatic structure,
R16 and R17 are independently hydrogen, methyl, ethyl, propyl, isopropyl, trifluoromethyl or optionally substituted phenyl, naphthyl or benzyl, or the substituents R16 1 5 and R17 taken together with the carbon atom to which they are attached form an optionally
substituted isoflavonoid ring system, and
the drawing represents either a single bond or a double bond; and
most preferably they have the following substituents wherein
RI is hydrogen,
R2, R3, R5, R6 and R8 are independently hydrogen, hydroxy, OR9, OC(O)Rq or methyl,
R4 and R7 are independently hydroxy, OR9 or OC(O)Rq,
R9 is methyl,
R13 is hydrogen, methyl, ethyl, trifluoromethyl, phenyl, chlorophenyl, nitrophenyl,
toluyl, naphthyl, benzyl, chlorobenzyl, nitrobenzyl or methylbenzyl,
R14 is hydrogen and R15 is hydrogen, methyl, ethyl, trifluoromethyl, phenyl, chlorophenyl, nitrophenyl, toluyl, naphthyl, benzyl, chlorobenzyl, nitrobenzyl or methylbenzyl, or the substituents R14 and R15 together with the nitrogen atom to which they are attached fonn an optionally substituted cyclic heteroalkyl or heteroaromatic structure,
- 14 R16 and R17 are independently hydrogen, methyl, ethyl, trifluoromethyl, phenyl, chlorophenyl, nitrophenyl, toluyl, naphthyl, benzyl, chlorobenzyl, nitrobenzyl or methylbenzyl, or the substituents R16 and R17 taken together with the carbon atom to which they are attached form an optionally substituted isoflavonoid ring system, and the drawing represents a single bond. Most preferably the novel aminated isoflavonoid of formula (I) are are compounds (1)
(14) as follows:
HO 0 HO 0
.0 OH N OH
HN HN
N02 2
HO 0 HO 0
SSN OH .0N OH
HN HN
CH3 3 4
1 5
- 15
HO @Ioo
HO %S OH
N
OH
5
j
HO 0
OH
HN
6 o-Cl
cl 7 m-Cl
8 p-Cl
HO 0 HO 0
N N

s OH s OH
HN HN
N
1
9 CN 10
- 16
HO 0 HO 0
OH SN OH
-S
H3C HO
12
CH3 CH3
HO 0 HO 0
OMe OMe
NH2 OMe H OMe
)zz:o
13 14
The compounds of the invention include all salts, such as acid addition salts, anionic salts and zwitterionic salts, and in particular include pharmaceutically acceptable salts. Chemical functional group protection, deprotection, synthons and other techniques known to those skilled in the art may be used where appropriate to aid in the synthesis of the 0 compounds of the present invention, and their starting materials. The preferred compounds of the present invention also include all derivatives with physiologically cleavable leaving groups that can be cleaved in vivo from the isoflavone or derivative molecule to which it is attached. The leaving groups include acyl, phosphate, sulfate, sulfonate, and preferably are mono-, di- and per-acyl oxy-substituted compounds, where one or more of the pendant hydroxy groups are protected by an acyl group, preferably an acetyl group. Typically acyloxy substituted isoflavones and derivatives thereof are readily cleavable to the corresponding hydroxy substituted compounds. In addition, the protection of Rmctional groups on the isoflavone compounds and derivatives of the present invention can be carried out by well established methods in the art, for example as described in T. W. Greene, Protective Groups in Organic Synthesis, John Wiley& Sons, New York, 198 1. Most preferred isoflavone and isoflavanone starting compounds contemplated for use in accordance with the invention include fornionone tin, biochanin, genistein, daidzein and equol, and functional derivatives, equivalents or analogues thereof Similarly important compounds are the isoflavone metabolites including **dihydrodaidzein** , cis- and transtetrabydrodaidzein and dehydroequol, and derivatives and **prodrugs** thereof. Chemical and functional equivalents of a particular isoflavone should be understood as molecules ex iting any one o more of the functional ac it es of the isoflavone and may be derived from any source such as being chemically synthesised or identified via screening processes such as natural product screening. The term "pharmaceutically acceptable salt" refers to an organic or inorganic moiety that carries a charge and that can be administered in association with a pharmaceutical agent, 1 5 for example, as a counter-cation or counter-anion in a salt. Pharmaceutically acceptable cations are known to those of skilled in the art, and include but are not limited to sodium, potassium, calcium, zinc and quaternary amine. Pharmaceutically acceptable anions are known to those of skill in the art, and include but are not limited to chloride, acetate, citrate, bicarbonate and carbonate. The term "pharmaceutically acceptable derivative" or "prodrug" refers to a derivative of the active compound that upon administration to the recipient, is capable of providing directly or indirectly, the parent

compound or metabolite, or that exhibits activity itself. As used herein, the terms "treatment", "prophylaxis" or "prevention", "amelioration" and the like are to be considered in their broadest context. hi particular, the term "treatment" does not necessarily imply that an animal is treated until total recovery. Accordingly, "treatment" includes amelioration of the symptoms or severity of a particular condition or preventing or otherwise reducing the risk of developing a particular condition. - 18 The amount of one or more compounds of formula (1) which is required in a therapeutic treatment according to the invention will depend upon a number of factors, which include the specific application, the nature of the particular compound used, the condition being treated, the mode of administration and the condition of the patient. Compounds of formula (1) may be administered in a manner and amount as is conventionally practised. See, for example, Goodman and Gihnan, "The pharmacological basis of therapeutics", 7th Edition., (1985). The specific dosage utilised will depend upon the condition being treated, the state of the subject, the route of administration and other well known factors as indicated above. In general, a daily dose per patient may be in the range of 0. 1 mg to 5 g; 1 0 typically from 0.5 mg to 1 g; preferably from 50 mg to 200 mg. The length of dosing may range from a single dose given once every day or two, to twice or thrice daily doses given over the course of from a week to many months to many years as required, depending on the severity of the condition to be treated or alleviated. It will be ftirther understood that for any particular subject, specific dosage regimens should be adjust over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Relatively short term treatments with the active compounds can be used to cause stabilisation or shrinkage of coronary artery disease lesions that cannot be treated either by angioplasty or surgery. Longer term treatments can be employed to prevent the development of advanced lesions in high-risk patients. The production of pharmaceutical compositions for the treatment of the therapeutic indications herein described are typically prepared by admixture of the compqunds of the invention (for convenience hereafter referred to as the "active compounds") with one or more pharmaceutically or veterinary acceptable carriers and/or excipients as are well known in the art. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the subject. The carrier or excipientmaybeasolidoraliquid,orboth,andispreferablyfonnulatedwiththe compound as a unit-dose, for example, a tablet, which may contain up to 100% by weight

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of the active compound, preferably from 0.5% to 59% by weight of the active compound. One or more active compounds may be incorporated in the formulations of the invention, which may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components, optionally including one or more accessory ingredients. The preferred concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. The formulations of the invention include those suitable for oral, rectal, ocular, buccal (for I 0 example, sublingual), parenteral (for example, subcutaneous, intramuscular, intradermal, or intravenous), transdermal administration including mucosal administration via the nose, mouth, vagina or rectum, and as inhalants, although the most suitable route in any given case will depend on the nature and severity of the condition

being treated and on the nature of the particular active compound which is being used.

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Formulation suitable for oral administration may be presented in discrete units, such as capsules, sachets, lozenges, or tablets, each containing a predetennined amount of the active compound; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. Such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active compound and a suitable carrier (which may contain one or more accessory ingredients as noted above). In general, the formulations of the invention are prepared by uniforrnly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the resulting mixture such as to form a unit dosage. For example, a tablet may be prepared by compressing or moulding a powder or granules containing the active compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound of the free-flowing, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid binder. - 20 Formulations suitable for buccal (sublingual) administration include lozenges comprising the active compound in a Ravoured base, usually sucrose and acacia or tragacanth; and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia. Formulations suitable for ocular administration include liquids, gels and creams comprising the active compound in an ocularly acceptable carrier or diluent. Compositions of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of the active compounds, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may 1 5 conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood. Injectable formulations according to the invention generally contain from 0. 1 % to 60% w/v of active compound and are administered at a rate of 0. 1 ml/minute/kg. Formulations suitable for rectal administration are preferably presented as unit dose suppositories. Formulations suitable for vaginal administration are preferably presented as unit dose pessaries. These may be prepared by admixing the active compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture. Formulations or compositions suitable for topical administration to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combination of two or more thereof. The active compound is generally present at a concentration of from
0.1%to5%w/w,moreparticularlyfromO.5%to2%w/w. Examplesofsuch compositions include cosmetic skin creams. - 21 Formulations suitable for transden-nal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally
bufferedaqueoussolutionofforexample,O.lMtoO.2Mconcentrationwithrespectto

the said active compound. See for example Brown, L., et al. (1998). Formulations suitable for transdennal administration may also be delivered by iontophoresis (see, for example, Panchagnula R, et al., 2000) and typically take the form of an optionally buffered aqueous solution of the active compound. Suitable formulations comprise citrate or Bis/Tris buffer (pH 6) or ethanol/water and contain from 0. 1 M to 0.2 M active ingredient. Formulations suitable for inhalation may be delivered as a spray composition in the form 1 5 of a solution, suspension or emulsion. The inhalation spray composition may Ruther comprise a pharmaceutically acceptable propellant such as carbon dioxide or nitrous oxide. The active compounds may be provided in the form of food stuffs, such as being added to, admixed into, coated, combined or otherwise added to a food stuff. The term food stuff is used in its widest possible sense and includes liquid formulations such as drinks including dairy products and other foods, such as health bars, desserts, etc. Food formulations containing compounds of the invention can be readily prepared according to standard practices. Therapeutic methods, uses and compositions may be for administration to humans or animals, including mammals such as companion and domestic animals (such as dogs and cats) and livestock animals (such as cattle, sheep, pigs and goats), birds (such as chickens, turkeys, ducks), marine animals including those in the aquaculture setting (such as fish, crustaceans and shell fish) and the like. - 22 The active compound or pharmaceutically acceptable derivatives prodrugs or salts thereof can also be co-administered with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, antiinflammatories, or antiviral compounds. The active agent can comprise two or more isoflavones or derivatives thereof in combination or synergistic mixture. The active compounds can also be administered with lipid lowering agents such as probucol and nicotinic acid; platelet aggregation inhibitors such as aspirin; antithrombotic agents such as cournadin; calcium channel blockers such as veraparnil, diltiazem, and nifedipine; angiotensin converting enzyme (ACE) inhibitors such as captopril and enalapril, and blockers such as propanolol, terbutalol, and labetalol. The compounds can also be administered in combination with nonsteriodal antiffiflaminatories such as ibuprofen, indomethacin, aspirin, fenoprofen, mefenamic acid, flufenamic acid and sulindac. The compounds can also be administered with corticosteroids. 5 The co-administration may be simultaneous or sequential. Simultaneous administration may be effected by the compounds being in the same unit dose, or in individual and discrete unit doses administered at the same or similar time. Sequential administration may be in any order as required and typically will require an ongoing physiological effect of the first or initial active agent to be current when the second or later active agent is administered, especially where a cumulative or synergistic effect is desired. The isoflavone and isoflavanone compounds for use in the preferred synthetic methods of the present invention may be derived from any number of sources readily identifiable to a person skilled in the art. Preferably, the isoflavones are obtained in the form of concentrates or extracts from plant sources. Again, those skilled in the art will readily be able to identify suitable plant species, however, for example, plants of particular use in the invention include leguminous plants. More preferably, the isoflavone extract is obtained from chickpea, lentils, beans, red clover or subterranean clover species and the like. Isoflavone extracts may be prepared by any number of techniques known in the art. For example, suitable isoflavone extracts may be prepared by water/organic solvent extraction - 23 from the plant source.

It will be appreciated that an isoflavone extract may be prepared from any single tissue of a single species of plant or a combination of two or more different tissues thereof. Similarly, an extract may be prepared from a starting material which contains a heterogeneous mixture of tissues from two or more different species of plant. Generally, where an isoflavone extract is prepared from plant material, the material may be comminuted or chopped into smaller pieces, partially comminuted or chopped into smaller pieces and contacted with water and an organic solvent, such as a water miscible organic solvent. Alternatively, the plant material is contacted with water and an organic solvent without any pre-treatment. The ratio of water to organic solvent may be generally in the range of 1: 1 0 to 1 0: 1 and may, for example, comprise equal proportions of water and solvent, or from 1 % to 3 0% (v/v) organic solvent. Any organic solvent or a mixture of suchsolventsmaybeused. Theorganicsolventmaypreferablybea C2-10,more preferably a C 1 -4 organic solvent (such as methanol, chloroform, ethanol, propanol, propylene glycol, erythrite, butanol, butanediol, acetonitrile, ethylene glycol, ethyl acetate, glycidol, glycerol dihydroxyacetone or acetone). Optionally the water/organic solvent mixture may include an enzyme which cleaves isoflavone glycosides to the aglycone form. The mixture may be vigorously agitated so as to form an emulsion. The temperature of the mix may range, for example, from an ambient temperature to boiling temperature. Exposure time may be between one hour to several weeks. One convenient extraction period is twenty-four hours at 90'C. The extract may be separated from undissolved plant material and the organic solvent removed, such as by distillation, rotary evaporation, or other standard procedures for solvent removal. The resultant extract containing water soluble and non-water soluble components may be dried to give an isoflavone-containing extract, which may be formulated with one or more pharmaceutically acceptable carriers, excipients and/or auxiliaries according to the invention. An extract made according to the description provided in the previous paragraphs may contain small amounts of oil which include isoflavones in their aglycone form (referred to herein as isoflavones). This isoflavone enriched oil, may be subject to BPLC to adjust the - 24 isoflavone ratios, or, if it is at the desired isoflavone ratio, may be dried, for example in the presence of silica, and be formulated with one or more carriers, excipients and/or auxiliaries to give an isoflavone containing extract. Alternatively, the isoflavones contained in said small amounts of oil may be further concentrated by addition to the oil of a non-water soluble organic solvent such as hexane, heptane, octane acetone or a mixture of one or more of such solvents. One example is 80% hexane, 20% acetone w/w having high solubility for oils but low solubility for isoflavones. The oil readily partitions into the organic solvent, and an enriched isoflavone containing extract falls out of solution. The recovered extract may be dried, for example in an oven at 50'C to about 120'C, and formulated with one or more pharmaceutically acceptable carriers, excipients and/or auxiliaries. It will be appreciated that the present invention also contemplates the production of suitable starting isoflavones, fimctional derivatives, equivalents or analogues thereof, by 1 5 established synthetic techniques well known in the art. See, for example, Chang et aL (1994) which discloses methods appropriate for the synthesis of various isoflavones as starting materials. Other suitable methods may be found in, for example, published International Patent Applications WO 98/08503 and WO 00/49009, and references cited therein, which are incorporated herein in their entirety by reference.

Cellular function

All cellularfanctions are under the control of a myriad of signals deriving from either distant cells (endocrine signals), neighbouring cells (paracrine signals) or from within the same cell (autocrine signals). These different signals work largely by stimulating the cell's genome (DNA) from where the appropriate cellular response is initiated. The process by which the signal is transmitted to the genome is known as signal transduction. By this we mean pathways, mostly involving different proteins, where activation of one protein catalyses the response of another protein, resulting finally in transcription of a particular gene or set of genes. Homeostasis, by which we mean the integrated functioning of cells, - 25 tissues and organs resulting in good health, is the end product of hundreds, possibly thousands, of different signals entering the body's cells on a continuous basis. From this signalling milieu, it is possible to divide signals arbitrarily into those that are related to a 'specialized function', and those that are related to the fundamental ability of the cell to exist and to function. Examples of 'specialized functions' are pain perception by a nerve cell, production of antibodies by an immune cell, detoxification reactions by a liver cell, or formation of urine by a kidney cell. Examples of 'fundamental functions' are cell survival or cell death, cell proliferation, cell migration, and angiogenesis. It can be seen that the key to regulating whether or not a cell is able to perfon-n 'specialized functions' is regulation of the cell's 'fundamental functions'. The applicants have found that compounds of the formula (1) regulate many of the 'fundamental functions'of the cell. The following are some examples of theTundamental

15 functions' that the inventors have found to be regulated by the aminated compounds of the present invention.

1 Cell survival/death
In order to continue to function, including the ability to respond to specialized functions, cells need to be continuously activating pro-survival signal transduction mechanisms. Prosurvival mechanisms act at two main levels - those that actively promote survival and those that actively suppress cell death (apoptosis). Pro-survival mechanisms involve a number of different signal transduction processes that ultimately cause transcription of certain genes whose end-products promote cell survival. These different processes involve, but are limited to, such molecular targets as MEK, ERK, and NFKB. Phenoxodiol has been found to operate across a range of these processes. One in particular by way of example is the enzyme, sphingosine kinase. Sphingosine kinase phosphorylates the substrate, sphingosine, to sphingosine-1-phos'phate.
Sphingosine-1phosphate is an important stimulator of pro-survival mechanisms and is over-expressed in - 26 a range of disease states characterized by increased longevity of cells. The aminated isoflavonoid derivatives down-regulate sphingosine kinase activity. Apoptosis can be achieved by a number of mechanisms as follows. (a) One such mechanism involves receptors known as 'death receptors'. These include receptors such as Fas/Mort, TGF and TNRF. Activation of receptors normally is suppressed through the production of blocking proteins such as G flip. The aminated isoflavonoid derivatives have been found to block the production of C-flip, in so doing, promoting the death of cells. (b) Another mechanism involves the activation of proteolytic enzymes known as caspases. Once activated, these enzymes autolyse the cell. The arninated isoflavonoid derivatives have been found to up-regulate the activity of caspases.
(c) Another mechanism involves disruption of mitochondria leading to the

production of various pro-death factors. The aminated isoflavonoid derivatives 1 5 have been found to promote such disruption through a direct and novel effect on the mitochondria. It can be seen from the above description, that the aminated isoflavonoid derivatives are able to induce cell death in a comprehensive manner via a number of different pathways. The ability of a single compound to have such broad and complementary effects is novel. But of considerable surprise is the finding that the aminated isoflavonoid derivatives exert such pro-death effects in abnormal cells only. That is, in non-nal healthy cells, the arninated isoflavonoid derivatives have no discernible effect on these regulatory processes. Cells that display abnormal activity of these regulatory processes include but are not limited to cells involved in such disease states as **cancer** , cardiovascular disease, autoimmune diseases, and diseases with immunological, inflammatory or hyperproliferative components. - 27

2 Cell proliferation
The ability to divide in response to growth signals is another fimdamental fimction required by normal, healthy cells. Sphingosine- 1 -phosphate appears to play a key role in facilitating the ability of cells to divide. The act of cell division involves a number of different enzymes as follows:
(a) the activation of topoisomerases (I and 11) whose task it is to organize DNA
prior to mitosis;
(b) the activation of cyclin dependent kinases (CDKs) whose task is it to move
the genome through the different stages of mitosis;
(c) inactivation of cyclin dependent kinase inhibitors (CDKIs) whose task it is to inhibit mitosis through suppression of CDKs. The aminated isoflavonoid derivatives surprisingly inhibit the 3 above enzyme systems, viz. topoisomerase 11, CKDs and CDKIs in cells that are behaving abnormally, particularly cells expressing abnormal prosurviving phenotype or aberrant cell proliferation.

3 Cell migration
It is well understood that the ability of a cell to migrate and to interact with its neighbouring cells is fandamental to health and disease. Sphingosine kinase and matrixmetalloproteases are key regulators of this important cell fimetion. The aminated isoflavonoid derivatives uniquely down-regulate both of these enzyme systems, thus diminishing the ability of cells in a diseased state to migrate.

4 Angiogenesis
The ability to form new blood vessels is well known to be a key event underlying many disease states associated with hyperplasia. Sphingosine kinase is a key facilitator of this event. The aminated isoflavonoid derivatives by down-regulating this enzyme, selectively impair angiogenesis when it occurs in association with disease, and not in healthy tissues. These broad-ranging effects of the aminated isoflavonoid derivatives on signal transduction mechanisms are complemented surprisingly by inhibitory effects on a wide - 28 range of enzymes, such enzymes not normally being regarded as part of signal transduction processes, but of the physiology of the body in more general terms. These effects also
include the following:

5 Steroido@enesis
The aminated isoflavonoid derivatives inhibit a number of enzymes involved in steroidogenesis. These include but are not limited to steroid dehydrogenase, 5-(X-reductase and aromatase. People skilled in the art would recognize that such effects would have significant impact on the production of steroid hormones including androgens, estrogens and corticosteroids. Such effects would be regarded as someone skilled in the art in having impact on the normal function of the male and female reproductive tissues including the breast, ovary, uterus, endometrium, cervix, vagina, prostate and penis. In summary, the inventors have surprisingly found that the aminated isoflavonoid derivatives regulate a unique collection of enzymes involved in both general metabolism and physiological function, and in signal transduction pathways that play pivotal roles in cell survival, cell growth, cell differentiation, and cell response to inflammation and immune modulators. Through regulation of this group of enzymes the compounds of the invention have the capacity to (a) to prevent or to treat many forms of disease irrespective of the cause or pathogenesis of that disease, and (b) influence the fall range of biological activities of the body's tissues and the way in which disease, age, envirom-nental influences and other drugs influence those activities. Moreover, it is highly surprising and novel to find that these compounds can cause a human breast **cancer** cell to undergo apoptosis and die, also can have such diverse effects as antagonising hypertension, redressing the immunological and inflammatory imbalance underlying inflammatory bowel disease, reversing Type 1 diabetes, and reversing male pattern baldness. - 29 It can readily be seen that the aminated isoflavonoid derivatives of the present invention and disorders as follows. 5 A. Diseases and disorders associated with abnonnal response to growth signals, abnormal cellular proliferation, dysfunctional gpoptosis, and abnormal migration patterns
(metastasis)
These include:

1 all forms of **cancer** (pre-malignant, benign and malignant) in all tissues of the body. hi this regard, the compounds may be used as the sole form of anti- **cancer** therapy,or in combination with other forms of anti- **cancer** therapy including but
not limited to radiotherapy and chemotherapy;

2 papulonodular skin lesions including but not limited to sarcoidosis, angiosarcoma, Kaposi's sarcoma, Fabry's Disease
1 5 3 .papulosquamous skin lesions including but not limited to psoriasis, Bowen's
Disease, and Reiter's Disease;

4 proliferative disorders of bone marrow including but not limited to megaloblastic disease, myclodysplastic syndromes, polycythemia vera, thrombocytosis and myelofibrosis;

5 hyperplastic diseases of the reproductive tract including but not limited to benign prostatic hyperplasia, endometriosis, uterine fibroids, and polycystic ovarian disease.
B. Diseases and disorders associated with abnormal angiogenesis
These include:

1 diseases and disorders associated with abnormal angiogenesis affecting any tissue within the body including but not limited to metastatic

cancers, psoriasis, hemangiomas and telangiectasia. C. Diseases and disorders associated with abnormal inflammatory/immunological reMonses
- 30
These include:
1 . diseases and disorders associated with inflammatory reactions of an abnormal or prolonged nature in any of the body's tissues including but not limited to rheumatoid arthritis, tendonitis, inflammatory bowel disease, ulcerative colitis,
Crohn's Disease, sclerosing cholangitis;

2 diseases and disorders associated with degenerative changes within the walls of blood vessels including but not limited to the syndrome known commonly as cardiovascular disease (embracing the diseases atherosclerosis, atheroma,
coronary artery disease, stroke, myocardial infarction, post-angioplasty restenosis, hypertensive vascular disease, malignant hypertension, thromboangiitis obliterans, fibromuscular dysplasia);

3 diseases and disorders associated with abnormal immunological responses including but limited to dermatomyositis and sclerodenna.
4 immunological imbalance including immune deficiency associated with HIV. or other viral infective agents or bacterial infective agents, and immune deficiency related to immaturity or aging. D. Diseases and disorders associated with decreased cellular fimction including dgpressed response to growth signals and increased rates of cell death
These include:

1 actinic damage characterized by degenerative changes in the skin including but not limited to solar keratosis, photosensitivity diseases, and wrinkling;

2 autoinimune disease characterized by abnormal immunological responses including but not limited to multiple sclerosis, Type 1 diabetes, systemic
lupus erythematosis, and biliary cirrhosis;

3 neurodegenerative diseases and disorders characterized by degenerative changes in the structure of the neurological system including but not limited to Parkinson's Disease, Alzheimer's Disease, muscular dystrophy, Lou
Gehrig Disease, motomeurone disease;
4 diseases and disorders associated with degenerative changes within the eye including but not limited to cataracts, macular degeneration, retinal atrophy. - 31 E. Diseases and disorders associated with dysfunctional or abnormal steroidogenesis
and function of rpproductive hon-nones
These include:

1 conditions in women associated with abnonnal estrogen/androgen balance including but not limited to cyclical mastalgia, acne, dysmenorrhoea, uterine
fibroids, endometriosis, ovarian cysts, premenstrual syndrome, acute menopause symptoms, osteoporosis, senile dementia, infertility;

2 conditions in men associated with abnormal estrogen/androgen balance including but not limited to benign prostatic hypertrophy, infertility,

gynecomastia, alopecia hereditaria and various other forms of baldness. The physiological effects ascribed to the aminated isoflavonoid derivatives of the invention particularly relate to the general areas of signal transduction pathways, anti- **cancer** 5 applications, anti-inflammatory activity and as cardio-protective agents. More particularly the aminated isoflavonoid derivatives of the invention show broad therapeutic indications including, and in particular, anti- **cancer** a@tivity via signal transduction inhibition, cell cycle regulation and apoptosis induction, antiangiogenesis (MMP inhibition), signal transduction perturbation (receptor protein tyrosine kinase inhibitor), COX inhibition, 5'alpha reductase inhibition, cardio protective properties and anti-inflammatory effects. - Specific areas of utility of the compounds of the present invention are described and exemplified as follows:

Anti- **cancer** :

In many western countries prostatic adenocarcinoma, secondary to lung **cancer** , is the most commonly diagnosed malignancy in men and the most common cause of death (Landis et al., 1999; Hsing et al., 2000). Established treatment options for localized prostate **cancer** , including surgery (radical prostatectomy) and radiation therapy, are curative in only 5278% of cases with the remaining proportion of cases suffering relapse due to residual disease (Morris and Scher, 2000; Papatsoris and Papavassiliou, 2001). VVhile androgens - 32 have an important role in controlling the growth of the normal prostate gland, they also promote onset of benign prostatic hyperplasia (BPH) and prostate **cancer** progression by transactivating cellular proliferation genes facilitate via the ligand bound androgen receptor (AR) (Amanatullah et al., 2000). Hence in early disease the mainstay of primary treatment options is androgen ablation therapy utilising both surgical and/or pharmacotherapeutic methods (Papatsoris and Papavassiliou, 2001). Interestingly epidemiological studies on the prevalence of prostate **cancer** in eunuchs, who have a deficiency in Talphareductase, show that this subset of the population have a very low incidence of the disease. In the androgen-signaling cascade 5'AR is responsible for the conversion of testosterone to dihydrotestosterone which, in comparison with testosterone, has a much stronger binding affinity for the AR and is able to elicit a stronger proliferative response (Papatsoris and Papavassiliou, 2001). As such considerable research effort has focused on defining novel'5'AR inhibitors. There are two isoforms of NADPH-dependent 5'alphareductase, termed types I and 11, with type I expressed primarily in human scalp, skin and liver, and type II expressed primarily in the prostate. Finasteride, a type 11 specific inhibitor, is the only available 5AR inhibitor to treat BPH, and early phase prostate **cancer** when used in combination with an anti-androgen (such as megestrol acetate). However, given the steroidal structure of finasteride and potential adverse effects, considerable research has focused onelucidating other nonsteroidal inhibitors of 5'alphareductase that are clinically acceptable (Chen, et al., 2001). Recent evidence infers that **cancer** initiation and progression may be facilitated via the excess production of prostaglandens in inflamed tissue (Vainio, 200 1). Cyclooxygenases (COX) catalyse the conversion of arachidonic acid (AA) to prostaglandins and thromboxanes. Supporting epidemiological studies in conjunction with laboratory studies provide strong evidence to suggest that traditional nonsteroidal anti-inflammatory drugs (NSAEDs including aspirin) and COX-2 inhibitors (celecoxib) may reduce the risk of colon **cancer** (Koki et al., 2002). Indeed clinical biopsies from many different malignancies consistently show a significant over-expression of COX The

presumed anti- **cancer** mechanism of action elicited by NSAMs is thought to be due to their ability to inhibit the production of prostaglandins via COX-2, which can drive angiogenesis and prevent apoptosis of **cancer** cells (Vaino, 2001; Fosslien, 2001.)
Anti-inflammatory:
Prostaglandins such as PGE2 and PG12 and thromboxanes (TXs) such as TXA2 are fatty acid derivatives known as eicosanoids (Penglis et al. 2000). They are involved in both
normal physiology and inflammatory responses. AA released from membrane phospholipids, is the primary substrate for COX enzymes thus giving rise to eicosanoids. Regardless of the COX isotype (COX 1 and COX 2) prostaglandin (PGH2) is the main intermediate of this reaction and it is the common precursor for downstream prostanoid production (PGE2, PG12 and TXA2).). The potential of a test agent to demonstrate antiinflammatory activity can be assessed by measuring the compound's ability to inhibit PG and TX synthesis in screening assays. The preliminary data presented in the Examples which follow on the aminated isoflavones of the invention and their ability to inhibit both 1 5 thromboxane synthase and COX support that this class of molecule has therapeutic application as an NSAID. The invention is ffirther illustrated by the following non-limiting Examples and accompanying drawings.
Example 1 - General Synthetic Methods

1 Imine synthesis
0 0
NH2R
0 N
R

2 Hydrazone synthesis
- 34
0 0
H2N-NR2
N
R2N

3 Semicarbizone synthesis
0 0
H2N N)@ NR2
H
N
HN
R2N 0

4 Azine synthesis
/NH2
N
0 0
R R
N
N
R)@ R
4.1 Azine dimer synthesis
0 0
H2N-NH2
2 x
0 ON

N
1 0 0
- 35
5 Oxime synthesis
0 0
H2NOR
0 N
0

6 Amine synthesis (Reductive)
0 0
NHR2
H2/Raney Ni
0 N
R/
R
In the above general methods, the structures may be optionally substituted with the desired substituents, or synthons or derivatives thereof The reactive amine compounds may be present as, for example, their hydrochloride salts and the reactions performed in the presence of a base such as sodium acetate, or as appropriate as deten-nined by a skilled synthetic chemist.
Synthesis
Dihydrodaidzein (1 mmol) was refluxed with 3 mole equivalents of the phenylhydrazine hydrochloride and 3 mole equivalents of sodium acetate (246 mmol) in 4 ml of methanol for 6 hours. The solution was filtered and the methanol removed under reduced pressure. The product was then purified by silica gel column chromatography (1 0% ether, 90% dichloromethane), yielding between 40% and 60% of the product.
AcO 0 H
H2N
0 R
OAc
HO 0
N
OH
HN
Cpd.1 R=H
Cpd. 2 R = p-NO2
Cpd. 3 R = p-CH3
R
R=H
H-NMR: (d6-acetone) 8.046(s), 8.018(s), 7.787(s), 7.194(t), 7.088(d), 6.762(m), 6.542(d of
d)@ 6.292(d)@ 4.400(d of d), 4.3165(d of d), 4.198(s)
CI-MS (+): 256
R = p-NO2
H-NMR: (d3-acetonitrile) 8.685(s), 8.638(s), 8.239(d), 8.079(d), 7.247(t), 7.046(m), 6.817(d of d), 6.60(d), 6.646(d), 6.583(d of d), 4.546(d), 4.392(d), 4.309(s)
CI-MS (+): 298
R = P-CH
H-NMR: (d3-acetonitrile) 8.028(s), 7.999(s), 7.689(s), 7.085(d), 7.000(d), 6.45(d), 6.529(d
of d), 6.285(d), 4.388(d of d), 4.321(d of d), 4.180(s), 2.220(s)
CI-MS(+): 361, 344, 256
In a similar way, the benzyl substituted compound 4, chloro phenyl

substituted compounds - 37 6-8, pyrido compound 9 and cyano compound 10 were also prepared. The dimeric compound 5 was prepared by standard azine synthesis. Reaction of dihydrodaidzein (1 mmol) with methylarnine (3 mmol) afforded the methyl imine compound 1 1. hi a similar way the hydroxy imine 12 was also prepared with hydroxylamine. Acylation of the amino derivative 13 from the reductive arnination (ammonia/H2/Raney 1 0 Ni) with 3 eq. acetic anhydride and mild acid work-up gave the N-acetyl derivative 14 in near quantitative yeild.

Example 2 - Methods

Cell cytotoxicity analysis:

The method of Alley et al. (1988) was followed. Briefly, prior to cytotoxicity screening a growth curve was constructed for each tumour line to be screened to determine growth kinetics, optimal seeding density to yield logarithmic growth over five days, and the corresponding lag time. Spent culture medium was aspirated from a sub-confluent adherent monolayer culture (T-75), the cells trypsinised and resuspended in a minimal volume of culture medium. After counting cells, a 96-well plate was seeded at an appropriate density (1 00 jkl) to yield optimal growth parameters and the plate was then incubated at 37'C under 5% C02. After the pre-determined lag-time the plate was treated with either vehicle (negative control) or serial dilutions of the test compound prepared in culture medium, and then incubated for a ffirther five days. MTT (0.5 mg/ml) prepared in PBS was added to all wells and incubated at 37'C for - 3hr. Spent medium was then carefully aspirated and DMS 0 (I 5 0 pd) was added to solublise cells and the reduced fon-nazan. Absorbance was then read on a SpectraMax plate reader at 570nm and viable cells in treated plates were expressed as a percentage of cells in control plates. - 38

Androgen inhibition studies:

The method of Negri-Cesi and Motta (1 994) and Negri-Cesi et al. (1 999) was followed. Briefly, LNCaP cells were cultured in RPMI supplemented with 10% fetal calf serum and 2 mM L-glutamine at 37'C under 5% C02. At day 0 a subconfluent LNCaP culture flask (80%) were harvested by trypsinisation, washed, resuspended in RPMI media completed with charcoal stripped fetal calf serum (RPMli) and seeded into 12 well plates at 30,000
cellsperwell(15,000cells/mL). Theplateswereculturedat37'Cwith5%CO2for48 hours. On day 2, spent media was carefully aspirated from all plates and then replenished with 2 ml RPME containing either testosterone (0.5 pM) as positive control, testosteione plus finasteride (luM) as inhibitor control and vehicle as growth control (equivalent concentration of DMSO). Test plates were treated as described above; only serial dilutions of test compounds prepared in RPME were used. Concentrations of test compound were chosen based on their cytotoxicity profile as determined in the cell cytotoxicity analysis 1 5 methods section above i.e. the top concentration used in the LNCaP proliferation assay was determined as the concentration at which cells first appear close to 100% viable along the cytotoxicity curve. This concentration was chosen to ensure that any inhibition of proliferation imparted by the test agent was due to the inhibition of 5'AR and not due to direct killing of the cells. It is important not to disturb cell monolayer during the addition of treatments. On days 5 and 8 the process followed on day 2 was repeated for all plates. On day 1 1 spent media was aspirated from all wells, cells were washed gently with PBS (500AI), trypsinised and the cells in each well counted using a haemocytometer. The average cell count and standard deviation was calculated and the result expressed as the % inhibition of testosterone-induced proliferation in comparison with vehicle control.

Thromboxane synthase and COX inhibition screening assays:
Human buffy coats were obtained from the Red Cross Blood Bank. Buffy coat (50 ml) was diluted 1:2 with sterile phosphate buffered saline (PBS), overlayed onto Lymphoprep density gradient medium and centrifuged at 800g for 20 min. The mononuclear cell PANQ layer was removed and washed with PBS and monocyte enriched cells were prepared from MNC by counter-current centrifugal elutriation. Monocytes were then resuspended in RPMI tissue culture medium with 10% foetal calf serum at 1.5 x 106 cells ml. Test analogues were prepared in DMSO and incubated with monocytes at 37' for 30 minateitherlOorlOO/.tM.
Afterthe3Ominpre-incubation,bacteriallipopolysaccharide (LPS) was added (200 ng/ml) and cells were incubated for a farther 18h at 37' in 5% CO2. After centrifugation, cell-free supernatants were then removed and assayed for either prostaglandin or thromboxane production, as determined by radioiramunoassay. Because TXA2 is labile in aqueous medium, TXB2, the stable hydrolysis product of TXA2, was measured. For each dose (0, 1 0, 1 001tM), incubations were performed in triplicate. Results are expressed as mean + SD, n7- ANOVA followed by Newman-Keuls multiple 0 comparisons test was used to examine differences between doses and the control values.
Cytotoxicity analysis:
Cpd. 1 and Cpd. 3 exhibited moderate anticancer activity with Cpd. 1 demonstrating activity against the prostate **cancer** lines LNCaP and DU-145 (Fig. 1A and 1B; Table 1.). 5 A slightly better IC50 was observed against the androgen-independent prostate **cancer** line DU-145 (13.81 /.tM) when compared with LNCAP (16.25 IzM), which is androgen responsive. Modest activity (>20 ItM) was also observed against the other cell lines tested. Like Cpd. 1, Cpd. 3 also exhibited moderate activity against LNCaP (16.26 ItM) (Fig 1C; Table 1.), however while demonstrating some efficacy against DU-145 (19.2 JtM), Cpd. 3 had activity against the large cell lung carcinoma line NCI-H460 (13.3 ItM) (Fig 1D and Table 1). Cpd. 3 had the best overall cell killing activity against all cell lines tested. In contrast to Cpd. 3, Cpd. 2, which has a nitro group instead of the methyl group in position 4 of the phenyl ring, had the lowest activity against all cell lines tested (Table 1).
Androgen hibibition Studies:
In both studies investigating testosterone-induced proliferation of LNCaP cells a two four fold induction was observed in the rate of growth of these cells in response to testosterone (Fig 2A and B). This testosterone-induced proliferation was potently blocked by finasteride (1 IzM) (Fig. 2A and B). Taken together these data demonstrate that the screening model is fanctioning. Of the 3 analogues tested, Cpd. 1 was the least potent (2.25 ItM) inhibitor of testosterone-induced proliferation, while Cpd. 3 exhibited a 3 fold - 40 better result (IC50 0.68 AM) over Cpd. 1 (Fig 2, 3 and Table 2). Cpd. 2 was the most effective analogue at inhibiting testosterone-induced proliferation, with no IC50 determined at 37 nM, which is some 60-fold more effect than Cpd. 1 (Fig 2, 3 and Table 2). It is noted that Cpd. 2 having an electron- withdrawing group (-NO2) in position 4 in comparison with an electron-donating group (-CH3) (Cpd. 3) enhances the inhibitory activity of the molecule in this particular assay.
Example 3 - Results and Discussions
Table 1. Cytotoxicity comparison of Cpd. 1, Cpd. 2 and Cpd. 3 against PC3 (AR negative prostate Ca), LNCaP (AR positive Prostate Ca), DU145 (AR negative prostate Ca), NMA
MB-468 (ER negative breast Ca) and NCI-H460 (large cell lung Ca)
Cell Line (u

Analogue	PC3		LNCaP		DU-145		MDA-MB-468		NCI-H460	
	Avg.	St.dev	Avg.	St.dev	Avg.	St.dev	Avg.	St.dev	Avg.	St.dev
Cpd. 1	33.9	2.26	16.2	.074	13.8	2.12	34.9	19.3	27.6	0.60
Cpd. 2	44.8	3.39	50.9	4.66	46.0	0.74	26.1	1.20	32.7	0.30
Cpd. 3	27.9	6.43	16.2	3.88	19.1	1.62	22.4	5.52	13.3	1.62

Table 2. Phenylhydrazone analogue inhibition profile of testosterone-induced LNCaP proliferation

Analogue	IC50 (uM)
Cpd. 1	2.25
Cpd. 2	ND @ 0.035
Cpd. 3	0.68

Inhibition of thromboxane synthase and COX:

Cpd. 1 and Cpd. 3 exhibited 1 00% inhibition of COX activity when assayed at 1 0 [LM, while Cpd. 2 inhibited this activity by 77% (Figure 4). Likewise, 1 0/,LM Cpd. 1, Cpd. 2 and Cpd. 3 inhibited thromboxane synthase by 33, 27 and 60% respectively but their inhibitory effect was less potent in comparison with their inhibition of COX. These data support the finding that the aminated isoflavone analogues are inhibitors of thromboxane synthase and COX and as such, molecules with this scaffold exhibit potential as antiinflammatory agents. In addition, therapeutic application as NSAIDS inhibition of COX - 41 activity supports that the phenylhydrazone analogues also exhibit anti- **cancer** activity. Cpd. 3 and Cpd. 1 were found to be the more effective anticancer agents with respect to their direct killing ability, however, they were less effective at inhibiting testosteroneinduced proliferation. The most effective analogue inhibiting testosterone-induced proliferation was Cpd. 2, which was the least effective analogue in the direct cell-killing assay. These results show that there are variations on the activities and modes of action in the two anti- **cancer** screens the test compounds were subjected to. Further, the ability of these aminated analogues to inhibit COX confirms that this class of molecule has multiple anti- **cancer** applications and their ability to inhibit thromboxane synthase suggests a role in anti-inflammation. The invention has been described herein, with reference to certain preferred embodiments, in order to enable the reader to practice the invention without undue experimentation. 1 5 However, a person having ordinary skill in the art will readily recognise that many of the components and parameters may be varied or modified to a certain extent without departing from the scope of the invention. Furthermore, titles, headings, or the like are provided to enhance the reader's comprehension of this document, and should not be read as limiting the scope of the present invention. The entire disclosures of all applications, patents and publications, cited herein, if any, are hereby incorporated by reference. Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds refeffed to or indicated in this specification individually or collectively, and any and all combinations of any two or more of said steps or features. - 42 The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any forrn of suggestion that that prior art forms part of the common general knowledge in the field of endeavour. - 43

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Claims

1 A compound of the general formula (1):

R8
R7 R1
R2
R6
R5 N R4
z R3

wherein

Rj@ R25 R3@ R45 R5@ R6@ R7 and R8 are independently hydrogen, hydroxy, OR9, OC(O)H, OC(O)Rq, OS(O)R% OSi(RIO)3, QO)Rii@ C02RI2, alkyl, haloalkyl, aryl, arylalkyl, thio, alkylthio, amino, alkylamino, dialkylamino, nitro or halo, or any two of the substituents R2 R3 and R4 together with tfie carbon atoms to which they are attached
form a cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl structure,
R9 is alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,
Rio is independently hydrogen, alkyl or aryl,
R11 is hydrogen, alkyl, aryl, arylalkyl, arylalkyl or an amino acid, and
R12 is hydrogen, alkyl, haloalkyl, aryl, arylalkyl or alkylaryl,

x is 0, NR12 ors,
z is R13, NR14R15, NR13CONR14R15, N=CR16RI7 or OR13,
R135 R14 and R15 are independently hydrogen, amino, thio, nitro, cyano, or optionally substituted alkyl, haloalkyl, acyl, aryl, heteroaryl, arylalkyl or alkylaryl, or the substituents R14 and R15 together with the nitrogen atom to which they are attached form an optionally substituted cyclic heteroalkyl or heteroaromatic structure, and
R16 and R17 are independently hydrogen, amino, thio, nitro, cyano, or optionally substituted alkyl, haloalkyl, acyl, aryl, heteroaryl, arylalkyl or alkylaryl, or the substituents R16 and R17 taken together with the carbon atom to which they are attached form an optionally substituted isoflavonoid ring system,
- 46 or when X is NR12, the substituent R12 may be a bond such that R8 and X together with the carbon atoms to which they are attached form one of the following structures:
R8 R8 R8
R7 N R,
R7 N Ri R7 R,
R Y R6 Y R Y
R5 I I
R5 N R5 N
z z z
where Y is
R2
R4
3
and wherein
R1, R2, R3, R4, R5, R6, R7, Rg and Z are as defined above, and
the drawing represents either a single bond or a double bond
which compounds include pharmaceutically acceptable salts and derivatives thereof

2 A process for the preparation of a compound of formula (I) compri@ing the step of
reacting the 4-keto group of a compound of the formula (X):
R8
R7 x R1
R2 (X)
R
R,5
R4
R3
wherein
R1, R2@ R3@ R41 R5@ R6@ R7@ R8 and X are as defined in claim 1, and
- 47
the drawing represents either a single bond or a double bond
with an aminating agent.
3 A method for the treatment, prophylaxis or amelioration of a disease or disorder which method includes the step of administering a therapeutically effective amount of one or more compounds of formula (I) or a pharmaceutically acceptable salt or derivative thereof to a subject.

4 A method for the treatment, prevention or amelioration of diseases associated with aberrant cell survival, aberrant cell proliferation, abnon-nal cellular migration, abnormal angiogenesis, abnormal estrogen/androgen balance, dysfimctional or abnormal steroid genesis, degeneration including degenerative changes within blood vessel walls,

inflammation, and immunological imbalance, which comprises administering to a subject one or more compounds of the formula (1) or a pharmaceutically acceptable salt or derivative thereof optionally in association with a carrier and/or excipient.

5 A method of inducing apoptosis in cells expressing abnormal prosurvival phenotype which comprises contacting said cells with one or more compounds of the formula (1) or a pharmaceutically acceptable salt or derivative thereof optionally in association with a carrier or excipient.

6 A method for inhibiting migration of cells having an abnon-nal cellular migration phenotype which comprises contacting said cells with a compound of the formula (1) or a pharmaceutically acceptable salt or derivative thereof optionally in association with a carrier or excipient. 1

7 A method for inhibiting angiogenesis in tissue expressing aberrant angiogenic phenotype which comprises contacting said tissue with a compound of the formula (I) or a pharmaceutically acceptable salt or derivative thereof optionally in association with a carrier or excipient. - 48

8 A method for the treatment, prevention or amelioration of **cancer** in a mammal which method comprises the step of bringing a compound of formula (1) or a pharmaceutically acceptable salt or derivative thereof into contact with cancerous tissue in a mammal that is suffering from a tumour, such that neoplastic development in said cancerous tissue is retarded or arrested.

9 Use of one or more compounds of fonnula, (1) or a pharmaceutically acceptable salt or derivative thereof in the manufacture of a medicament for the treatment of a disease or disorder.

10 Use of a compound of formula (I) or a pharmaceutically acceptable salt or derivative thereof as an anti-inflammatory agent.

11 An agent for the treatment, prophylaxis or amelioration of a disease or disorder, which agent comprises one or more compounds of formula (1) or a pharmaceutically acceptable salt or derivative thereof.

12 A pharmaceutical composition which comprises one or more compounds of formula (1) or a pharmaceutically acceptable salt or derivative thereof in association with one or more pharmaceutical carriers, excipients, auxiliaries and/or diluents.

13 A drink or food-stuff, which contains one or more compounds of formula (I) or a pharmaceutically acceptable salt or derivative thereof.

14 A compound of formula I or a pharmaceutically acceptable salt thereof as herein described with reference to the Examples and/or accompanying drawings.

- end of record -

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Display 9/7/38 (Item 13 from file: 349)
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00435422 **Image available**

NOVEL COMPOUNDS USEFUL AS THERAPEUTIC AGENTS AND ASSAY REAGENTS

NOUVEAUX COMPOSES UTILES COMME AGENTS THERAPEUTIQUES ET COMME REACTIFS D'ANALYSE

Patent Applicant/Assignee:
RILEY Patrick Anthony,
PHOTIOU Andrew,
KHAN Tariq Hussain,
OSBORN Helen Mary Isted,
Inventor(s):
RILEY Patrick Anthony,
PHOTIOU Andrew,
KHAN Tariq Hussain,
OSBORN Helen Mary Isted,

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AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW GH GM KE LS MW SD SZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
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English Abstract

Novel pro-drugs and assay reagents are provided which are useful as therapeutic agents especially for delivery and targetting therapeutically active agents to melanoma cells. The pro-drugs and assay reagents are substrates for tyrosinase and may be represented by the formula TyrX-B-ThrAg*. The compounds of formula TyrX-B-ThrAg* are capable of releasing a therapeutically active agent or assayable substance (ThrAg) at a desired location, TyrX- being a residue of an optionally substituted tyrosine analogue.

French Abstract

L'invention concerne de nouveaux precurseurs de medicaments et de nouveaux reactifs d'analyse qui sont utiles en tant qu'agents therapeutiques, en particulier pour amener des agents therapeutiquement actifs, de maniere ciblee, aux cellules d'un melanome. Les precurseurs de medicaments et les reactifs d'analyse sont des substrats pour la tyrosinase et ils peuvent etre representes par la formule TyrX-B-ThrAg*. Les composes de cette formule TyrX-B-ThrAg* sont capables de liberer un agent therapeutiquement actif ou une substance (ThrAg) d'analyse a l'emplacement souhaite. Tyr-X est un reste d'un analogue de la tyrosine, qui peut eventuellement etre substitue.

Claim

CLAIMS

1. A pro-drug which is capable of releasing a therapeutically active agent at a desired location, characterised in that the pro-drug is a substrate for tyrosinase wherein in the presence of tyrosinase, the prodrug is oxidised to a quinone, which undergoes cyclisation and hydrolysis to release therapeutically active agent.
2. A compound which is capable of conversion to an assayable substance such as an indicator molecule, characterised in that the compound is a substrate for tyrosinase wherein in the presence of tyrosinase, the compound is oxidised to a quinone, which undergoes cyclisation and hydrolysis to release said assayable substance.

3. A compound which is capable of releasing a therapeutically active agent or assayable substance (ThrAg) at a desired location, characterised in that the
compound is a substrate for the tyrosinase enzyme and has the formula:
TyrX-B-ThrAg
wherein TyrX- is a residue of an optionally substituted tyrosine analogue of the
structure
RI.(, Y
, n
R5
wherein each of the symbols =Z- is independently selected from =CH-, =C-, =N-, and -N+=O,
B represents a linking group or single bond linking TyrX and ThrAg*,
ThrAg * represents a residue of a therapeutically active agent ThrAg or a residue of an indicator molecule, and
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n is 1, 2, 3 or 4 (preferably 1 or 2),
and either NQ- represents -N- and the dotted line represents a bond linking
the nitrogen atom to the indicated ring atom
or NQ- represents -NR 6- and the dotted line is to be ignored,
R' and R2 independently represent hydrogen, halogen (e.g. F, Cl, Br or I) or -OH, R3, R4, and R5 independently represent hydrogen, halogen (e.g. F, Cl, Br or I), C1.4
alkyl, C1
4 alkenyl, CF3, NO2, -OH,- COOH, -COOR, or -CH2OH,wherein R
represents C1
4 alkyl, and
R6 represents hydrogen, halogen (e.g. F, Cl, Br or I), C1
4 alkyl, C1
4 alkenyl, CF3,
NO2, -OH, -COON, -CH2OH, -COOR, -OR, -SR or -SeR wherein R represents
C1
4 alkyl,
and wherein in the presence of tyrosinase, the compound TyrX-B-ThrAg * is oxidised to a quinone, which undergoes cyclization and hydrolysis to release ThrAg.
4. A compound according to Claim 3 wherein B represents
O O S O S
C- C-O- C- C-NH- or C-NH
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5. A compound according to Claim 3 having the formula
n

ZoZ

6. A compound according to Claim 3 having the formula

7. A compound according to Claim 3 having the formula
wherein = Z-, R, and R2 are as defined in Claim 3.

8. A compound according to any of Claims 3 to 7 wherein R, and R2 are selected from H and OH.

9. A compound according to to any of Claims 3 to 8 wherein R3 and R4 are selected from H and CH3.
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10. A compound according to any of Claims 3 to 9 wherein R1, R2 , R3 , R4, R5 and R6 are hydrogen.

11. A compound according to any preceding claim wherein n is 1.

12. A compound according to any preceding claim wherein B represents a single bond.

13. A compound according to any of Claims 3 to 12 wherein the therapeutically active agent has the formula NH2-ThrAg*.

14. A compound according to any of Claim 3 to 12 wherein B represents NH-CO-.

15. A compound according to any of Claims 3 to 12 wherein the therapeutically active agent has the formula HO-ThrAg*.

16. A compound according to any preceding claim having one of the following
formulae:
HO O O 1
H 'N-"DRUG
O<<

O DRUG DRUG
HO
O,N ; R HO
DRUG HO HO
HO NH
/R
HO
DRUG HO
Y DRUG
O
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HO
HO
DRUG

17. A compound according to Claim 3 having one of the following formulae
HO H
HO CH O N 3 DRUG HO O DRUG

18. A compound according to any of claims 1 to 13 wherein THrAg is a cytotoxic drug.

19. A compound according to any of Claims 3 to 18 which is a prodrug.

20. The use of a pro-drug as claimed in Claim 1 or Claim 19 in the manufacture of a pharmaceutical composition for treating melanoma.

21. The use of a compound according to any of Claims 2 to 16 in an assay procedure for detecting the presence of tyrosinase enzyme in tissue samples and body fluids.
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- end of record -

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Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements
Setchell, Kenneth D R; Brown, Nadine M; Desai, Pankaj; Zimmer-Nechemias, Linda; Et al
Journal of Nutrition (IJNU), v131 n4S, pS1362-S1375, p.14
Apr 2001
TEXT:
Bioavailability of Pure Isoflavones in Healthy Humans and Analysis of Commercial Soy Isoflavone Supplements1,2

ABSTRACT The pharmacokinetic behavior of naturally occurring isoflavones has been determined for the first time in healthy adults. We compared plasma kinetics of pure daidzein, genistein and their beta-glycosides administered as a single-bolus dose to 19 healthy women. This study demonstrates differences in the pharmacokinetics of isoflavone glycosides compared with their respective beta-glycosides. Although all isoflavones are efficiently absorbed from the intestinal tract, there are striking differences in the fate of aglycones and /3-glycosides. Mean time to attain peak plasma concentrations (t
sub max
) for the aglycones genistein and daidzein was 5.2 and 6.6 h, respectively, whereas for the corresponding /-glycosides, the t
sub max
. was delayed to 9.3 and 9.0 h, respectively, consistent with the residence time needed for hydrolytic cleavage of the glycoside moiety for bioavailability. The apparent volume of distribution of isoflavones confirms extensive tissue distribution after absorption. Plasma genistein concentrations are consistently higher than daidzein when equal amounts of the two isoflavones are administered, and this is accounted for by the more extensive distribution of daidzein (236 L) compared with genistein (161 L). The systemic bioavailability of genistein [mean AUC = 4.54 (mu)g/(mL x h)] is much greater than that of daidzein [mean AUC = 2.94 (mu)g/(mL x h)], and bioavailability of these isoflavones is greater when ingested as 0-glycosides rather than aglycones as measured from the area under the curve of the plasma appearance and disappearance concentrations. The pharmacokinetics of methoxylated isoflavones show distinct differences

depending on the position of the methoxyl group in the molecule. Glycitin, found in two phytoestrogen supplements, underwent hydrolysis of the p-glycoside moiety and little further biotransformation, leading to high plasma glycitein concentrations. Biochanin A and formononetin, two isoflavones found in one phytoestrogen supplement, were rapidly and efficiently demethylated, resulting in high plasma genistein and daidzein concentrations typically observed after the ingestion of soy-containing foods. These differences in pharmacokinetics and metabolism have implications for clinical studies because it cannot be assumed that all isoflavones are comparable in their pharmacokinetics and bioavailability. An analysis of 33 phytoestrogen supplements and extracts revealed considerable differences in the isoflavone content from that claimed by the manufacturers. Plasma concentrations of isoflavones show marked qualitative and quantitative differences depending on the type of supplement ingested. These studies indicate a need for improvement in quality assurance and standardization of such products. J. Nutr. 131:1362S-1375S, 2001.

KEY WORDS: * phytoestrogens * isoflavones * pharmacokinetics * soy foods * supplements * humans * blood

Interest in soy isoflavones has exploded in the past 5 y after a wealth of scientific data showing that these phytoestrogens possess potent and wide-ranging biological activities. Much of this interest has been directed to the area of women's health and is stimulated by promising preliminary data from clinical studies showing the effectiveness of phytoestrogen-rich soy protein-containing foods in a range of hormone-dependent conditions [reviewed recently by Setchell (1998) and Setchell and Cassidy (1999)]. There is compelling evidence from studies of animal models and in vitro assay systems that isoflavones have significant direct and indirect hormonal and nonhormonal effects of relevance to human disease prevention or treatment (Adlercreutz 1995, Barnes 1995, Barnes et al. 1994, Barnes and Peterson 1995, Kim et al. 1998, Setchell and Adlercreutz 1988).

The discovery of very high urinary concentrations of isoflavones in adults who consume soy protein and the evidence supporting their biological potency are probably the prime reasons that the soybean has been elevated to the rank of a functional food. The recent approval by the Food and Drug Administration (November 10, 1999; No. 279) to allow a cardiovascular health claim for foods that contain at least 6.25 g of soy protein/serving will undoubtedly lead to a large increase in the sales of soy-fortified foods and the constituent isoflavones. The impact of this ruling is already evident because the food industry has seized the opportunity to label soy products with the isoflavone content, as well as the soy protein content, even though the former is not required under the food-labeling laws.

More disturbing, however, is the plethora of dietary supplements of isoflavones that have flooded the market, with wideranging claims and little regulation regarding their manufacture or efficacy. There is a paucity of information regarding the bioavailability, metabolism and clinical effectiveness of dietary isoflavone supplements, and in many cases, the consumer may simply be generating very expensive urine. Until proved otherwise, it cannot be assumed that a dietary isoflavone supplement will behave in the same manner as an isoflavone-rich food, and up to this point, there is a lack of information on isoflavone pharmacokinetics. In this report, we determined for the first time the pharmacokinetics of individual purified soy isoflavones in healthy subjects to assess the bioavailability of daidzein and genistein and their respective beta-glycosides. We also analyzed a range of dietary isoflavone supplements for their isoflavone content using liquid chromatography and mass spectrometry techniques and compared the observed concentrations with the

manufacturer's claim of content. The fate of the methoxylated isoflavones such as glycitin, a main component of many phytoestrogen supplements, and formononetin and biochanin A, the constituent isoflavones of clover supplements sold to women for the relief of menopausal symptoms, were examined. We also bioassayed the estrogenicity of one supplement that claims to enhance breast size in women through its phytoestrogen content. The findings raise serious concerns regarding some of the marketing ploys that promote isoflavone supplements and speak to the need of more rigorous policing of these products along the guidelines for pharmaceutical agents.

METHODS

Pharmacokinetics and apparent bioavailability of individual isoflavones in healthy adults: study design

Nineteen healthy premenopausal women aged >=18 y were recruited for pharmacokinetic studies that were carried out using the resources of the National Institutes of Health-funded General Clinical Research Center at Children's Hospital Medical Center in Cincinnati, Ohio. Subjects were excluded if they had preexisting chronic renal, liver, pulmonary or cardiovascular disease; had been administered antibiotics within the preceding 3 mo; or were taking oral contraceptives. At the time of the study, the prohibitive costs and limited availability of the glycoside conjugates restricted the determination of pharmacokinetics to only a small number of women. The lack of prior quantitative data for plasma concentrations of these compounds precluded performing accurate power calculations to establish the optimal sample size for the comparison of different isoflavone forms. The number of subjects enrolled was based on the feasibility of analytically handling the large numbers of plasma sampies collected; the study was therefore observational. The Human Investigations Review Board of Children's Hospital Medical Center approved the study protocol, and informed consent was obtained from each subject.

The study subjects were divided into four groups, and they consumed daidzein (n = 6), genistein (n = 6), daidzin (n = 4) or genistin (n = 3). Subjects were asked to abstain from foods containing soy protein for >=1 wk before and during the study. Each subject fasted overnight and then consumed a standardized 50-mg dose of the isoflavone together with a drink and followed by breakfast. This dose was chosen because it was considered at the time within the expected range of isoflavone intake by persons consuming soy as a staple food and was the approximate level of intake previously shown to have endocrine effects in healthy premenopausal women (Cassidy et al. 1994).

Blood samples (5 mL) were obtained via venipuncture before (baseline) and then after 2, 4, 6, 8, 12 and 24 h in all subjects and, in some, after 48 h. Blood was obtained via an indwelling catheter for the more frequent samplings and/or via Vacutainer for the later sample times depending on the choice of the individual. Blood samples were centrifuged, and the plasma was separated and immediately frozen at -20 deg C before analysis of isoflavone concentrations.

Pharmacokinetics of methoxylated isoflavones glycitin, formononetin and biochanin A

The pharmacokinetics of three methoxylated isoflavones were examined in one healthy man with the identical protocol. Glycitin (25 mg), the beta-glycoside of glycitein, was administered orally as a single-bolus dose, and blood samples were collected. After a 2-wk washout period, a mixture of formononetin and biochanin A, contained in a tablet of the over-the-counter supplement Promensil (40 mg total isoflavones per capsule), was then consumed orally as a single dose, and blood samples were obtained according to the protocol above. Plasma concentrations of the methoxylated isoflavones and their demethylated metabolites were measured

in the blood by gas chromatography-mass spectrometry (GC-MS).

Determination of isoflavones in plasma and urine bY GC-MS

The concentrations of daidzein, genistein, glycitein, biochanin A, formononetin and equol were measured by GC-MS using two stable isotopically labeled internal standards, and an isoflavone homologue as a second internal standard. These internal standards were added to the plasma prior to its extraction and work-up. Total and individual isoflavones were determined after extraction and enzymatic hydrolysis of the conjugates with a combined sulfatase and glucuronidase enzyme preparation. Unconjugated isoflavones were determined separately after group separation from their respective glucuronide and sulfate conjugates on a lipophilic anion exchange gel (Axelson and Setchell 1980). After equilibration of the plasma (0.25-0.50 mL) with 100-ng amounts of the internal standards [

sup 13

C]daidzein, [

sup 13

C]genistein and 7,4'-dihydroxyflavone, the sample was diluted with 10 volumes of 0.5 mol triethylamine sulfate/L (pH 5.0) and heated to 64 deg C before passage through a wetted solid-phase C18Bond Elut cartridge. The solid-phase cartridge was then washed with distilled water (10 mL), and isoflavones and their conjugates were recovered by elution with methanol (5 mL). The methanol extract was evaporated to dryness under nitrogen, reconstituted with 0.5 mol acetate/L buffer (pH 4.5) and hydrolyzed at 37 deg C overnight with a solution of 10,000 Fishman Units of a mixed beta-glucuronidase/sulfatase (Helix pomada; Sigma Chemical Co., St. Louis, MO) that was prefiltered through a cartridge of C18-Bond Elut to remove naturally occurring isoflavones in the enzyme preparation. After hydrolysis, isoflavones were isolated by solid-phase extraction on a C18-Bond Elut cartridge as described earlier. The phenolic isoflavones were separated from neutral compounds and purified by passage of the sample through a small column bed (7 x 0.4 cm) of triethylaminohydroxypropyl Sephadex LH-20 (TEAP-LH-20) prepared in the [OH-] form and packed in methanol. The phenolic compounds were recovered by elution of the gel bed with 15 mL of methanol saturated with CO2 (Axelson and Setchell 1980). The phenolic fraction was taken to dryness under a stream of nitrogen gas, and isoflavones were converted to the tert-butyldimethylsilyl (t-BDMS) ether derivatives for analysis by GC-MS. t-BDMS ethers were prepared by the addition of acetonitrile (100 (mu)L) and N-methyl-N-t-butyldimethylsilyltrifluoroacetamide in 1% t-butyldimethylchlorosilane (100 (mu)L), and the sample was heated at 65 deg C for 2 h. The reagents were removed by evaporation in a stream of nitrogen, and the derivatives were dissolved in hexane (100 (mu)L).

Determination of unconjugated isoflavones in plasma. The concentrations of individual unconjugated isoflavones were determined separately after solid-phase extraction of the plasma and omission of the hydrolysis step. Group fractionation and isolation of unconjugated nonsteroidal phenolic compounds were achieved through lipophilic anion exchange chromatography on TEAP-LH-20. In this system, the glucuronide and sulfate conjugates are retained on the get because of their lower pKa

sub at

and the unconjugated isoflavones are eluted with methanol saturated with CO2 (15 mL). This fraction was then evaporated to dryness, and the t-BDMS ether derivatives were prepared.

GC-MS conditions. Isoflavone t-BDMS ethers were separated and quantified by GC-MS. Chromatographic separation was achieved on a DB-1 fused silica capillary column (30 m X 0.25 mm i.d., 0.25-(mu)m film thickness; J & W Scientific, Folsom, CA) using helium as the carrier gas

(flow rate, ~2 mL/min) and with a temperature program that increased from 2600 to 310'C in increments of 10 deg C/ min. Selected ion monitoring GC-MS of specific and characteristic ions in the electron ionization (70 eV) spectra of the t-BDMS ether derivatives of each isoflavone permitted highly sensitive and specific quantification. The following ions were monitored: m/z 425 (daidzein and 7,4'-dihydroxyflavone internal standard), mh 426 ([sup 13 C]daidzein), mh 470 (equol), m/z 555 (genistein), m/z 556 ([sup 13 C]genistein), mh 455 (glycitein), ra/z 382 (formononetin) and m/z 455 (biochanin A). The individual isoflavones were quantified by comparing the peak area in the specific ion channels at the correct retention time determined from authentic compounds with the peak area response for the internal standard. This area ratio was then interpolated against calibration curves constructed for known amounts (0-200 ng) of the individual isoflavones. Concentrations were expressed in ng/mL for individual plasma isoflavones.

The within day reproducibility for repeat analysis of the same plasma sample was 0.5% for daidzein and 1.0% for genistein. The mean between-batch reproducibility determined over a 18-month period of 19 separate runs where duplicate plasma samples were assayed was 5% (range 1.0-11.9%) for daidzein and 7% (range 1-17%) for genistein at concentrations of 100-200 ng/mL. The precision of equol measurements was 10% at a concentration of 5-7 ng/mL.

Determination of plasma isoflavone pharmacokinetics. A noncompartmental approach was used for the pharmacokinetic analysis with WinNonlin 1.5 (Pharsight Corporation, Mountain View, CA) computer software. This approach uses the trapezoidal rule for the determination of area under the plasma concentration-time curve (AUC). The total AUC (AUC sub O-->inf| or AUC sub inf) is calculated in a two-step process. In the first step, AUC from time point 0 to any time point t on the log-linear region of the terminal part of the curve is determined. The remaining area from t to infinity is determined as C sub t /A sub z , where C sub t is the plasma concentration of the isoflavone at time t and the rate constant is calculated from the slope of the terminal phase of disposition. At least three points were included for the purpose of lambda sub z determination. The number of points to be included was based on the correlation coefficient and residual analysis. Appropriate weighting schemes, with weights of 1/y or 1/y sup 2 , where y represents the observed concentration, were used to improve the goodness-of-fit of the data. Other parameters that were determined included peak plasma isoflavone levels (C sub max), time required to achieve the peak levels (t sub max), systemic clearance (normalized to the bioavailable fraction) and volume of distribution normalized to the bioavailability fraction (F) Vd/F. AUC

sub inf
, t
sub max
, t
sub 1/2

of elimination and Vd/F reflect the systemic exposure to the isoflavone, rate of absorption, rate of elimination and the extent of isoflavone distribution in the body, respectively.4 While the exact bioavailable fraction could not be determined in our experiments, comparison of AUCs, Vd/F and CL/F of the isoflavones facilitated a comparative evaluation of the apparent bioavailability (or systemic exposure), extent of distribution and the rate of elimination, respectively.

Analysis of soy isoflavone supplements by HPLC and electrospray-mass spectrometry

Qualitative and quantitative analyses of 33 commercially available isoflavone supplements or extracts were performed with HPLC and electrospray ionization LC-MS (ESI-MS). These supplements were obtained from various sources in the United States and elsewhere, and the following products were analyzed: #1, Carlson Easy Soy and #2, Carlson Easy Soy Gold, (J. R. Carlson Laboratories, Inc, Arlington Hts., IL); #3, Erdic-Busting Out (Cerdic B.V. 6718TBEde, The Netherlands); #4, Estroven, (AMERIFIT, Bloomfield, CT); #5, Genistein, Soy Isoflavone Extract (Solgar Laboratories, Leonia, NJ); #6, Kudzu Root Extract (Solaray, Inc., Park City, UT); #7, Healthy Woman, (Personal Products Co., Skillman, NJ); #8, One a Day, Menopause Health, (Bayer Corp., Consumer Care Division, Morristown, NJ); #9, PhytoEstrin (USANA, Inc., Salt Lake City, UT); #10, Phyto Soya, (Arkopharma, Coulsdon, Surrey. UK); #11, Soy Extract (Enzymatic Therapy(R), Green Bay, Wisconsin); #12, Nature's Herbs Phytoestrogen Power, (Alvita(R) a TWINLAB(R) Division, Quality Drive, American Fork, UT); #13, Promensil, (Novogen, Inc., Stamford, CT); #14, PhytoEstrogen, Solaray, (Nutraceutical Corp. for Solaray, Inc., Park City, UT); #15, Soya Isoflavones, Holland and Barrett Ltd., Nuneaton, England; #16, Soyamax (USANA, Inc., Salt Lake City, UT); #17, Soy Care, S.C.P.I., Waltham, MA; #18, Nature's Resources Soy Isoflavones, Mission Hills, CA; #19, Soy Plus--Dr. Art Ulene's Phyto-protein formula, Feeling Fine Co., Marina del Rey, CA; #20, Naturally Preferred Soy Germ, Inter-American Products, Ohio; #21, Trinovin, Novogen Inc., Stamford, CT.; #22, Basic's Soy Isoflavones, Basic Drugs. Inc. Vandalia, OH; #23, Flash Fighters, Nature's Bounty, Bohemia, NY; #24, Menopause Balance, Walgreens, Deerfield, IL; #25, Novasoy, Archer Daniel Midland, Decataur. IL; #26, New Phase-Sunsource, Chatham Inc., Chattanooga, TN; #27, Spring Valley Phytoestrogen Complex, NaturPharma, American Fork, UT; #28, Sundown-Soy Isoflavones, Sundown Vitamins, Boca Raton, FL; #29, Phytosoy, Nature's Sunshine, Spanish Fork, UT; #30, Soy Choice, Vitanica, Sherwood, OR; #31, Revival, Physician's Laboratory, Walkertown, NC; #32, Nutrisoy Flour, Archer Daniel Midland, Decataur. IL; #33, Soy Life 25, Schouten USA Inc., Minneapolis, MN.

Four tablets or capsules of each supplement were analyzed separately. The supplements were ground to a very fine powder using a small coffee grinder, and the isoflavones were extracted from an accurately weighed portion of each by refluxing the sample in 80% methanol (50 mL) for 1 h. After being filtered through Whatman No. 1 filter paper, the aqueous methanolic phase was made up to a fixed volume of 100 mL, and the internal standard equilenin (60 (mu)g) was added to 1.0 mL (1/100th) of this extract. This was then used for direct HPLC and ESI-MS analyses.

Extracts of the soy supplements were analyzed on a Waters Alliance 2690 HPLC system. The sample size injected was 10 (mu)L, at a flow rate of

1.0 mL/min, and UV absorbance was monitored at 260 nm using a Waters 2487 UV detector. Separation of the individual isoflavones was accomplished on a 250 X 4.6-mm ODS (C18) reversed phase HPLC column (Keystone Scientific, Bellefone, PA). The column was eluted with a water/acetonitrile gradient. The mobile phase was 100% of 10 mmol ammonium acetate/L [0.1% trifluoroacetic acid (TFA)] held isocratic for the first 2 min and then decreased to 50% in a constant gradient from 2 to 24 min and then finally held isocratic period with 50% acetonitrile and 50% 10 mmol ammonium acetate/L (0.1% TFA) for 5 min, before being returned to the original composition of 100% 10 mmol ammonium acetate/L (0.1% TFA).

ESI-MS was performed on a Micromass Quattro LC/MS. The HPLC effluent to the ESI probe was split 10:1. The desolvation temperature was 300 deg C, and the source temperature was 100 deg C. The sampling cone was held at 50 V, and the extractor was held at 2 V. Data were collected in the positive ion mode. Table 1 lists the [M + H]+ ions that were monitored for the phytoestrogens and their conjugates.

Only the isoflavones that could be positively identified with ESI-MS were quantified. Isoflavone content was established by comparing the isoflavone peak area ratio with the internal standard equilinen and through interpolation against calibration plots constructed of known quantities of the pure compounds. Reproducibility of the method was established from intrabatch replicate analyses of 12 samples of one supplement (#7) and found to be 2.7% for the total concentration (coefficient of variation). Interbatch precision when two different soy extracts were used as quality control samples was 5-6% (coefficient of variation).

Bioassay for estrogenicity in the phytoestrogen supplement Erdic

A classic in vivo bioassay for estrogenicity was performed on one of the supplements (Erdic, also sold under the name "Busting Out" in the United States) to test for the presence of biologically active phytoestrogens that might not have been detected on HPLC analysis. This supplement was chosen for analysis because of our failure to confirm the manufacturer's claims that it contains "natural phytoestrogens" that help to enhance a woman's breast size. Four 70-dold female and two young adult male Sprague-Dawley rats were obtained from Charles Rivers Laboratory, placed on AIN-930 diet [a soy-free diet designed for pregnant or lactating dams and growing pups; Reeves (1993)] and bred in-house. After breeding, the females were housed individually and maintained on the AIN-930 diet until the pups were weaned. On parturition, litters were reduced to 10 pups per dam. On d 20 after parturition, the pups were weaned, and the female pups from each litter were randomly distributed to one of three different treatment groups, for a total of six weanlings per group. The groups were fed one of the following diets:

Food supplement. Erdic tablets and AIN-93G pellets were reduced to powder, and the Erdic powder was added to pellet powder at a ratio of 20% of the test supplement (by weight) to 80% of the AIN-93G. The two components were mixed by rotation for a minimum of 3 h and supplied in a feeding jar to six 20-d-old weanlings on d 20-23.

Control group A. The positive control group of six weanling rats were fed powered AIN-93 to which 160 ttg estradiol 3-benzoate (Sigma Aldrich, St. Louis, MO) had been added per 100 g of feed (Odum et al. 1997). This was mixed by rotation as described and supplied ad libitum to the weanling rat pups on d 20-23.

Control group B. This control group consumed powered AIN93G only, supplied ad libitum on d 20-23.

Beginning on d 19, before the pups were removed from the dam, they were weighed and assigned to their test group. On d 20, they were weaned and housed two to four per cage; daily weights were taken throughout the

experiment. On d 23, the pups were killed by COZ inhalation, the uterus was removed and a wet weight was obtained. The uteri were then dried at 70 deg C overnight to constant weight, and the dry weight was recorded.

RESULTS

Plasma kinetics of isoftavones

Daidzein. The individual and group mean plasma daidzein appearance and disappearance curves for women administered a single bolus dose of 50 mg of daidzein are shown in Fig. 1. The profiles were similar for all women. The curves were characterized by a rapid increase in plasma isoflavone concentrations followed after ~2 h by a slight decline and then a second rise that attained a mean maximum plasma concentration at time (t
sub max
) 6.6 1.36 h. At this time, the mean maximum plasma daidzein concentration (C
sub max
) was 194 +/- 30.6 ng/mL (0.76 +/- 0.12 (mu)mol/L). Pharmacokinetic analysis of the plasma curves showed the half-life of elimination to be 9.34 +/- 1.3 h for daidzein. The AUC was 2.94 +/- 0.22 (mu)g/(mL - h), and the mean plasma clearance was 17.5 +/- 1.4 L/h. The average volume of distribution normalized to apparent bioavailable fraction Vd/F; where F is the bioavailability fraction (V
sub dt
, Vd/F) for daidzein was large at 236.4 +/- 35.9 L. Daidzein predominantly circulated in plasma in the conjugated form. Unconjugated daidzein concentrations were relatively low after the administration of a 50-mg dose of the aglycone. In the first 2 h, the proportions of unconjugated daidzein increased and accounted for 8.4 +/- 0.9% of the total daidzein, but once steady state was established, the unconjugated daidzein fraction constituted an average of 2.7 +/- 03%. A true elimination phase for both aglycones was not detected because of the extensive persistence and steady-state levels of the unconjugated daidzein in plasma, which made it difficult to accurately determine pharmacokinetic parameters, including t
sub 1/2
of elimination.

Genistein. The individual and group mean plasma genistein appearance and disappearance curves for women administered a single-bolus dose of 50 mg of genistein are shown in Fig. 2. The plasma profiles were similar for all of the women. The early kink in the absorptive phase of the individual plasma curves seen for daidzein was less evident for genistein. The mean t
sub max
for peak plasma concentration occurred 9.33 +/- 1.33 h after administration of the single-bolus oral dose, with a mean C
sub max
for genistein of 341 +/- 74 ng/mL (1.26 +/- 0.27 /mol/L). Pharmacokinetic analysis of the disappearance curves showed the half-life of elimination of genistein to be 6.78 +/- 0.84 h. The AUC of the plasma concentrations was 4.54 +/- 1.41 (mu)g/(mL x h). The mean plasma clearance normalized to the bioavailable fraction (CL/F) of genistein was 18.3 +/- 5.7 L/h, and the average V
sub d
was 161.1 +/- 44.1 L. As seen for daidzein kinetics, the unconjugated genistein concentrations in plasma were very low, accounting for only 3.7 +/- 1.1 % in the first 2 h and 1.6 +/- 0.1% once steady state had been established. Although there was an increase in unconjugated genistein after administration of the aglycone, the steady-state and persistent low levels in the elimination phase precluded the calculation of pharmacokinetics.

Glycosides daidzin and genistin. Figure 3 shows the plasma appearance and disappearance curves for daidzein and genistein measured in premenopausal women after they received a single-bolus dose of the glycoside conjugate of either daidzin (n = 4) or genistin (n = 3). These curves displayed characteristics similar to those of the corresponding aglycones. However, the time to attain maximum plasma daidzein and genistein concentrations (t
sub max
) was longer at 9.0 +/- 1.0 and 9.3 +/- 1.3 h, respectively, after the glycosides were ingested. The Cma for daidzein after administration of its glycoside conjugate was 394 +/- 61 ng/mL (1.55 +/- 0.24 (mu)mol/L), whereas the Cm.. for genistein after genistin was ingested was 341 +/- 127 ng/mL (1.22 +/- 0.47 (mu)mol/L). For daidzin pharmacokinetics, the t
sub 1/2
was 4.59 +/- 0.5 h, whereas the corresponding value for genistin administration was 7.0 +/- 0.76 h. The Vd/F for genistin was 112.3 +/- 34.5 L, and its clearance was 10.8 +/- 2.2 L/h. When daidzin was administered, AUC was 4.52 +/- 0.49 (mu)g/ (mL x h). The CL/F for daidzin was 11.6 +/- 1.6 L/h, and its Vd/F was 77 +/- 14 L. The apparent bioavailability for genistin calculated AUC of genistin was 4.95 +/- 1.03 (mu)g/(mL x h). These values closely parallel the corresponding values for aglycone administration. Unconjugated daidzein and genistein in plasma accounted for 1.7 +/- 0.4% and 1.5 +/- 0.2% of the total isoflavones during the first 2 h, respectively, and for 1.1 +/- 0.2% and 1.1 +/- 0.45 once steady-state had been attained, indicating extremely efficient first-pass conjugation after intestinal hydrolysis of the glycoside moiety. Pharmacokinetics were not determined for the plasma unconjugated fractions.

Formation of metabolites-equol production

FIGURE 1

TABLE 1

Equol, an important intestinal bacterial metabolite of daidzein, was expectedly not detected in significant amounts in the plasma of women who consumed genistein (or genistin, because it is a specific metabolite of daidzein). Surprisingly, it was not found in the plasma of the women who ingested daidzein, but it did appear in the plasma of two of the four women who consumed daidzin. The plasma profiles (Fig. 4) show that there is a time lag in its appearance and that after a single-- bolus ingestion, it takes at least 6-8 h before equol appears in substantial amounts in plasma. This observation is consistent with a distal or colonic origin for its formation. At the time of this study, the metabolites of genistein, were unavailable as a standard and consequently not measured in the plasma samples from this study.

Pharmacokinetics of methoxylated isoflavones glycitin, formononetin and biochanin A

The pharmacokinetics of glycitin (7,4"-dihydroxy-6-methoxyisoflavone-7-D-glucoside) was examined in one healthy man according to the same protocol as that described for daidzein and genistein. Glycitein appeared rapidly in plasma after the administration of a single-bolus dose of 25 mg of its beta-glycoside. Peak plasma concentration was reached 4 h after oral ingestion, and thereafter plasma concentrations declined, with an elimination t
sub 1/2
of 8.9 h. The CL/F for glycitein was 32.1 L/h, and its AU 62 was 0.7 (mu)g/(mL x h).

The Vd/F for glycitein was relatively high at 415 L. There was a small rise in the plasma concentration of daidzein after the administration of glycitin, but overall the plasma profiles indicated there was negligible

biotransformation of glycitin, other than initial hydrolysis of the glycosidic group. Demethoxylation to daidzein was clearly a minor biotransformation pathway. (Fig. 5).

The behavior of a supplement containing methoxylated isoflavones from clover was examined in the same healthy adult by oral administration of a single tablet of the commercially available supplement Promensil (Novogen). HPLC analysis of this supplement (Fig. 6) showed that it contained predominantly formononetin and biochanin A in the aglycone form, but there were minor amounts of the glycosides of these methoxylated isoflavones, as well as daidzein and genistein. Overall, our analysis showed excellent agreement with the manufacturer's claim for composition. The oral administration of one tablet of Promensil led to a rapid increase in the plasma concentrations of daidzein and genistein (Fig. 5). These were the major isoflavones appearing in plasma, and they accounted for >95% of the total isoflavones measured. Although increases in the plasma concentrations of formononetin and biochanin A were observed, these were minor compared with the plasma appearance of the demethylated metabolites, daidzein and genistein. Due to the complexity of the mixture administered and because values were for just one subject, the pharmacokinetics were not determined, but overall it was evident that in contrast to glycitin, very little of the methoxylated isoflavones survived intestinal bacterial demethylation.

FIGURE 2

FIGURE 3

FIGURE 4

FIGURE 5 FIGURE 6

Qualitative and quantitative analyses of commercially available phytoestrogen supplements

Thirty-three commercially available phytoestrogen supplements or extracts were analyzed for isoflavone content by HPLC and ESI-MS. Only peaks that could be positively confirmed from their mass spectra were quantified. Individual concentrations of the aglycones and the various glycosides are summarized in Table 2. These are expressed as mg/g and are not corrected for the aglycone equivalency because this appears to be the manner in which most manufacturers are labeling these products. There was a large variability in the composition of these supplements as demonstrated from just four of the HPLC profiles shown in Fig. 6 and Fig. 7. Each of the 33 supplements revealed a different profile, and many contained an abundance of peaks of unknown origin and chemical structure. Overall, it was evident that these supplements could be broadly grouped into three main categories: 1) those in which the amounts of glycoside and aglycone forms of daidzein plus glycitein exceeded genistein by >2.0 fold and 2) those in which this ratio was < 1.50 and only small proportions of glycitein and its glycosides were present. Supplements that contained high levels of glycitin and glycitein were apparently manufactured from extracts of the soy germ, as this is a major isoflavone of the soybean hypocotyl, 3) those made from extracts of clover and containing mainly methoxylated isoflavone (Fig. 7).

The methoxylated clover isoflavones were major components of several of the supplements that we analyzed (Promensil). Tea made from red clover is available in health food stores but on analysis (data not shown) was found to contain very low levels of isoflavones. The Chinese plant kudzu is also available as an extract, and this was shown to contain high levels of the isoflavone glycoside puerarin but only low levels of daidzein and genistein. Because puerarin glycoside was not available to us as a pure standard, its concentration in the kudzu extract was not accurately determined, and therefore our measurement of isoflavone content of products containing kudzu is underestimated. The concentrations of isoflavones expressed on a per-gram basis of the product are summarized in Table 2. The

isoflavone content per capsule or tablet as judged by our analytical methods compared with the respective claim made by the manufacturer is given in Table 3. It was evident that many of the commercial supplements contained levels of isoflavones that, based on our analysis, are not in accord with the manufacturer's claim. One of these (Erdic) was found to contain insignificant amounts of phytoestrogens.

Plasma isoflavone concentrations resulting from food and supplement sources of isoflavanes

Two supplements selected at random and a soy-containing food (So Good soy milk; Sanitarium Health Food Company, Berkeley Vale, New South Wales, Australia) were each consumed by six healthy adults (three men and three women) during a 5-d period with a washout of 5 d between successive intakes of the products. Fasting blood samples were obtained for the determination of plasma daidzein and genistein concentrations. The results show the contrasting effect on plasma isoflavone concentrations of different supplements (see Fig. 8). One of the supplements (labeled B), containing 21 mg isoflavones, resulted in very high plasma daidzein concentrations and a relatively low genistein level. The mean ratio of plasma daidzein to genistein during steady state was 5.08. Administration of the other supplement (labeled A) led to a reversal of this ratio (0.65), so genistein was the major isoflavone in plasma. The plasma profile of supplement A was qualitatively similar to that obtained when most soy-containing foods are consumed. Soy-containing foods typically lead to higher plasma genistein concentrations (Fig. 8).

In vivo estrogenicity of the breast-enhancing supplement Erdic

In an attempt to determine whether there was any estrogenic activity in one of the supplements that was found by HPLC to contain insignificant levels of isoflavones yet claimed to have phytoestrogens to enhance the breast size of women, the supplement was tested for its estrogenicity using an in vivo bioassay. Body weight gains were similar for all rats in the three diet groups: the control diet (AIN-93G), the estradiol-- spiked AIN-93G diet and the AIN-93G diet containing 20% Erdic supplement (Fig. 9). There was no significant difference in the weights of the rats assigned to the three different groups on d 19 or 20 of life. Between d 20 and 21, when the pups were weaned and adjusting to the new diets, mean body weight increased from 52 to 53 g only in the pups fed the powdered AIN-93G diet. The mean body weight of the rats fed the AIN-93G with added estradiol remained constant (52 g), whereas those fed the AIN-930 with added Erdic supplement declined significantly ($P < 0.05$) from 53 to 50 g during this short period. Within 24 h (by d 22), the mean body weight of all three groups increased and continued to do so through d 23. There were no significant differences among the final mean body weights of the rats in the three groups (Fig. 9). When uterus weight was measured and expressed in terms of wet weight and dry weight, no significant differences in mean uterine weight were observed between the AIN-93G controls Erdic fed rats. However, the wet and dry uterine weights of positive controls fed AIN-93G containing estradiol increased significantly ($P < 001$) compared with the controls (AIN93G) and those fed AIN-93G with 20% Erdic added (Fig. 9).

DISCUSSION

The hormonal potency of dietary isoflavones first became apparent in the 1940s when their abundance in species of clover (Trifolium spp.) caused a devastating infertility syndrome in sheep grazing in pastures in which this clover was prevalent (Bennetts et al. 1946). Interestingly, isoflavones from extracts of clover constitute one commercially available phytoestrogen supplement targeted at postmenopausal women for the relief of menopausal symptoms. The majority of the phytoestrogen supplements, however, are derived from soybeans, and to a lesser extent from extracts of

the Chinese vine Kudzu (Keung 1993, Keung and Vallee 1998). All of the supplements we analyzed are commercially available as overthe-counter products, and presently, there is limited regulation of the supplement industry because these products fall under the scrutiny of the Dietary Supplement Health and Education Act of 1994. More disturbing is the fact that there are virtually no data on the pharmacokinetics, pharmacology or safety of phytoestrogen supplements, and many of the health claims that drive supplements sales are based on clinical and nutritional data from phytoestrogen-rich foods, such as soy, rather than from supplements.

It has been known for >60 y that soybeans contain very high concentrations of isoflavones (Walz 1931). However, the full impact of these compounds in human nutrition did not become apparent until the chance observation that persons consuming soy-containing foods excreted isoflavones in the urine at levels far exceeding endogenous estrogen concentrations (Axelson et al. 1984, Setchell et al. 1984). This intriguing observation led to the hypothesis that soy isoflavones would have beneficial effects in protecting against many hormone-dependent conditions because of their partial estrogen antagonist and agonist properties (Setchell et al. 1984). Animal studies, supported by in vitro data, have demonstrated the anticancer properties of isoflavones (Adlercreutz 1995, Barnes 1998, Barnes et al. 1990, Fournier et al. 1998, Messina et al. 1994), and there is vast literature to confirm that isoflavones have a number of nonhormonal properties of relevance to disease prevention (Kim et al. 1998, Setchell 1988). The animal data have been increasingly supported by clinical trials that established the physiological effects of isoflavones in areas such as cardiovascular health, menopause and **cancer** (reviewed recently in Setchell 1998 and Setchell and Cassidy 1999). The recent Food and Drug Administration approval of a cardiovascular health claim for soy protein through its ability to lower blood cholesterol concentrations will inevitably bring isoflavones into mainstream consumer circles (November 10, 1999, No. 279). Not unexpectedly, the consumer can find a plethora of supplements being marketed in different forms and compositions and with various health claims. It is evident from our study that for a high proportion of these products, the consumer should have little confidence in what they are purchasing. Regrettably, there is a paucity of data to confirm that isoflavone supplements are as nutritionally effective as isoflavone-rich foods, and several recent studies have shown that isoflavones in the form of supplements are ineffective in lowering serum cholesterol concentrations (Hodgson et al. 1998, Nestel et al. 1997 and 1999).

The Vd/F was large for both daidzein and genistein, indicating extensive tissue distribution. Isoflavones have been found to be concentrated in the human breast, appearing in nipple aspirates (Petrakis et al. 1996), whereas studies with rats have shown they rapidly partition into the brain (Lephart et al. 2000, Setchell 1998). Daidzein exhibited a much higher Vd/F than genistein (236 L for daidzein versus 161 L for genistein), and this explains why genistein levels in plasma always exceed daidzein concentrations when equivalent amounts of the two isoflavones are ingested. For most foods, genistein and its glycosides tend to be present in higher levels than daidzein and its glycosides, and therefore clinical feeding studies should always reveal a higher plasma genistein concentration than daidzein. This has been our experience to date.

TABLE 2

FIGURE 7

With regard to metabolism, we measured equol, the bacterially derived metabolite of daidzein (Axelson et al. 1982, Setchell et al. 1984), in the

plasma but did not measure desmethylangolensin, or dihydrodaidzein (Bannwart et al. 1984, Kelly et al. 1993) because these studies predated interest in these metabolites and standards were not available to us. Equol was the first isoflavone to be identified in human urine and blood, and its discovery led to the identification of soy as a rich source of isoflavones (Axelson et al. 1982, Setchell et al. 1984). In the early studies, it was found that two thirds of adults who consumed soy-containing foods converted daidzein to equol (Setchell et al. 1984). This ability to convert daidzein into equol led to use of the term "converters" to describe persons who have the necessary bacterial enzymes or intestinal conditions to make this biotransformation. Over time, the proportion of "converters" in a population seems to have decreased for some unexplained reason, and several groups have reported that only one third of the population are converters (Cassidy et al. 1994, Kelly et al. 1993, Sathyamoorthy and Wang 1997). Methods for measuring isoflavones have evolved since their initial discovery in urine, and the question of whether equol is being lost or missed in the work-up procedures is a valid one. The GC-MS techniques we use consistently find equol as the major circulating isoflavone of rats and mice (Brown and Setchell 2001); hence, the methodology used in our laboratory is excluded as an explanation for the differences. Whether the proportion of converters show geographical differences is unknown; the early studies were of adults living in Britain (Setchell et al. 1984), whereas those reported here are of U.S. adults. The makeup of the diet can alter the metabolism of isoflavones in the intestine. In experiments using an in vitro colonic fermentation system, it was found that under a high carbohydrate environment, fermentation was stimulated, and this increased the rate of conversion of daidzein to equol (Cassidy 1991, Setchell 1998, Setchell and Cassidy 1999). Virtually no conversion occurred when a low carbohydrate milieu was mimicked in vitro. This was also shown to be the case in a human study where greater equol production was seen with a diet that was higher in carbohydrates (Lampe et al. 1998). This suggests that the overall composition of the diet may have to be taken into consideration in clinical studies investigating the potential efficacy of isoflavones. In the "acute" studies described here, we found equol in the plasma of only three of nine adults fed its precursors, daidzin or daidzein. None of the subjects fed the aglycone showed equal in the plasma, and this was somewhat surprising. It is possible that this is explained by the aglycone being absorbed passively in the proximal small intestine, whereas the glycoside would not be taken up by the enterocyte, thus becoming delivered to the distal small intestine and colon for metabolism by bacteria. The observed time delay of at least 6-8 h before any equal appears in the plasma of those converters would be consistent with the bacterial enzymes being of colonic origin. Because the binding affinity of equal for the estrogen receptor is an order of magnitude greater than that of its precursor, daidzein (Shutt 1976, Shutt and Cox 1972) and because its protein binding to serum SHBG and albumin is much lower (Nagel et al. 1998), equal has greater estrogenic potency than daidzein. There may therefore be advantages to improve the intestinal conversion of daidzein to equal.

Although these studies define for the first time the plasma pharmacokinetics of pure isoflavones in healthy adults, similar data on isoflavone supplements are lacking, and there is little incentive under the Dietary Supplement Health and Education Act of 1994 for commercial manufacturers of these supplements to obtain this type of information. Our studies of a selection of commercially available over-the-counter phytoestrogen supplements show that there is a wide variation in composition and that no two supplements appear to be the same. This poses some difficulties for the consumer as to what supplement is "best" to

purchase. All vary in the amount of isoflavone that is "packaged" in the capsule, tablet or powdered extract, and there is no consensus on standardization of an appropriate or optimal dose. It is evident that the qualitative compositions of the isoflavone supplements are broadly divided into those that use soy germ as an ingredient and those that use isolate, or some other plant source, such as clover or kudzu. Some are clearly blends of several ingredients. Many of the supplements we analyzed had high levels of glycitin, a 6-O-methoxylated isoflavone glycoside. Little is known about its biological properties or bioavailability relative to other isoflavones, but based on its chemical structure, it is predicted to be less estrogenic than daidzein or genistein. Feeding studies have been carried out in humans with soy germ, which has a high glycitin content, and glycitein was identified in plasma up to 24 h later (Zhang et al. 1999). The pharmacokinetics of glycitin and glycitein are unknown. When pure glycitin was ingested as a single-bolus dose by one healthy man, its aglycone glycitein, rapidly appeared in the plasma with peak plasma concentrations occurring 4 h after ingestion. Other than hydrolysis of the sugar moiety, glycitin appears to undergo limited further biotransformation. Plasma daidzein levels do show a small increase 12 h after the ingestion of glycitin, indicating minor demethylation that undoubtedly occurs in the colon. Steric hindrance of the 6-methyoxyl group by the 7-hydroxyl in the structure of glycitein is presumed to account for the lack of intestinal bacterial conversion to daidzein. By contrast, the B-ring methoxylated isoflavones of clover, formononetin and biochanin A, structurally exhibit no steric hindrance, so these are rapidly and efficiently demethylated, giving rise to daidzein and genistein, respectively, in humans. Less than 5% of the methoxylated isoflavones remain intact, and this product effectively makes bioavailable the isoflavones that characterize soy proteins. The fate of isoflavones in clover extracts such as Promensil is consistent with the known metabolism of formononetin and biochanin A in sheep and several other animal species (Lindsay and Kelly 1970, Lundh 1995, Lundh et al. 1988). Formononetin and biochanin A show extremely poor affinity for the estrogen receptor (Shutt 1976, Shutt and Cox 1972). Molecular modeling studies show the 4'-hydroxyl on the B-ring of isoflavones to be the binding site for the estrogen receptor (Brzozowski et al. 1997, Pike et al. 1999), and therefore the presence of a methyl group markedly reduces estrogenic potency. The conversion of clover isoflavones to isoflavones typical of soy that clearly occurs when this supplement is ingested can be considered advantageous because it is difficult to understand the physiological advantages of the consumption of methoxylated isoflavones other than using these as a form of **prodrug** (precursor) for the delivery of **genistein** and **daidzein** .

FIGURE 8

FIGURE 9

The starting materials used to manufacture phytoestrogen supplements will have a significant effect on the ultimate bioavailability and characteristics of the circulating isoflavone levels. We demonstrated that two different supplements yield quite different plasma isoflavone profiles (Fig. 8). Those that incorporate the soy germ as a starting material result in plasma that is enriched in daidzein and low in genistein. By contrast, when the supplement is made from an extract of soy protein, the plasma is enriched to a greater extent in genistein. Plasma concentrations of genistein are typically higher than those of daidzein when soy protein foods are consumed, as is evident when these subjects consumed a soy milk drink (Fig. 8). Such differences make it impossible to compare data from clinical studies where sources of isoflavones are from foods or supplements unless plasma isoflavones are monitored. This is rarely done. Thus,

depending on the clinical effect being sought, the type of supplement may strongly influence the end point. For **cancer** prevention, higher plasma genistein concentrations may be advantageous, whereas for cardiovascular protection, the maintenance of higher antioxidant activity by sustained high concentrations of daidzein may be preferable. These are the types of issues and discrepancies that need to be resolved for the design of clinical studies in which phytoestrogens are investigated.

We found, based on our methodology using HPLC with the addition of an internal standard for quantification and ESI-MS for positive identification of each component, that approximately half (16/31) of the supplements had isoflavone levels that deviated by more than 10% from the claimed value. This is not surprising, because discrepancies in the contents of other herbal supplements have been described. In the case of one phytoestrogen product, Erdic (Busting Out), we found virtually no detectable isoflavones in the tablets, yet this product is marketed to women to enhance breast size, and its product literature and Internet Web site, claimed it was a good alternative to silicone implants for breast augmentation. At the time of these studies, it was being sold for $1485 for a 6-mo supply with the statement that, "Compared to the cost of implants ($4,000 and up) and the safety factor, this is a great product." Women were instructed to take "10 tablets a day or more." The product information under the section "How Does It Work?" indicated that the mechanism of breast enhancement occurred because "The Erdic product has natural estrogenic properties from plant sources (phytoestrogens) which promote tissue development". We failed to identify significant levels of phytoestrogens of the isoflavone class or for that matter any other similarly related compounds. The possibility that there may be other phytoestrogens present was considered, especially since one of the ingredients of the product is hops. Endocrine disruption has been noted in female hop workers and attributed to 8-prenylnaringenin, which binds to estrogen receptors with greater affinity than isoflavones (Milligan et al. 1999). Therefore, we subjected this supplement to bioassay for estrogenicity. When fed to immature rats at a level of 20% of the diet, there was no detectable increase in uterine weight consistent with a lack of significant estrogenicity. In the absence of clinical data to the contrary, there must be serious doubt that this product will achieve the effects claimed for it. This specific example illustrates the sort of problems in an industry that is poorly regulated.

So far, there is little evidence that isoflavone supplements have the same clinical effects as phytoestrogen-rich foods, and whether this relates to differences in their bioavailability or metabolism remains unknown. Three recent studies have found that isoflavones have no effects on lowering serum cholesterol (Hodgson et al. 1998, Nestel et al. 1997 and 1999), yet a comprehensive clinical study of the effects of soy protein containing different levels of isoflavones has shown a dosedependent effect of isoflavones on reducing LDL cholesterol concentrations (Crouse et al. 1999). In connection with lipidlowering, it appears that the presence of a protein matrix is necessary for the effectiveness of isoflavones. Much work is needed to better understand the mechanism behind such a phenomenon. Isoflavone supplements are in large part being targeted to postmenopausal women for the relief of hot flushes. Clinical studies show that they have a modest effect on hot flushes that exceeds the placebo response, but they are not as effective as hormone replacement therapy. (NAMS Consensus Opinion 2000)

Finally, the safety of phytoestrogen supplements should be addressed. The misconception that it is safe if it is "natural" is a widely held belief. Many of the supplements analyzed contained numerous compounds that we could not identify, and nothing is known about these components of these

mixtures. With supplementation, the dangers of overdosing becomes a reality. Although diets rich in phytoestrogens have been consumed by millions of humans for millennia, the amounts ingested daily, estimated at 15-50 mg (Chen et al. 1999, Nagata et al. 1999, Wakai et al. 1999) are below the dose promoted for supplementation, and in some cases, fortified functional foods. It is known that deleterious effects can result from high levels of isoflavones fed to animals (Bennetts et al. 1946, Leopold et al. 1976, Setchell et al. 1987), and there is little reason to believe that adverse effects could not occur in humans as a result of excessive intakes.

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3 To whom correspondence should be addressed at Clinical Mass Spectrometry, Children's Hospital Medical Center, 3333 Burnet Avenue, Cincinnati, OH 45229. E-mail: SETCKO@chmcc.org

4 Abbreviations: AUC, area under the plasma concentration-time curve; C

sub max

, peak plasma isoflavone level; ESI, electrospray-mass spectrometry; GC, gas chromatography; MS, mass spectrometry; t

sub max

, time required to achieve the peak levels; TFA, trifluoroacetic acid; V

sub d

, volume of distribution normalized to the bioavailability.

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Kenneth D. R. Setchell,*3 Nadine M. Brown,* Pankaj Desai,** Linda Zimmer-Nechemias,* Brian E. Wolfe,* Wayne T. Brashear,* Abby S. Kirschner,* Aedin Cassidy

and James E. Heubi

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     Divisions of *Clinical Mass Spectrometry and
     Gastroenterology and Nutrition, **Department of Pediatrics, Children's
Hospital Medical Center and College of Pharmacy, University of Cincinnati
College of Medicine, Cincinnati, Ohio 45229 and
     Department of Nutrition, University of Surrey, Guildford, U.K.
       Copyright American Institute of Nutrition Apr 2001

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Set     Items   Description
S1       1007   (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES
            OR DIHYDROISOFLAVONE OR DAIDZEIN OR GENISTEIN OR GLYCITEIN) -
           AND (PRODRUG OR PRODRUGS OR PRO()DRUG OR PRO()DRUGS)
S2          3   S1 AND DT=REVIEW
S3          3   RD (unique items)
S4       4867   (PRODRUG OR PRODRUGS) AND DT=REVIEW
S5          2   S4 AND (DAIDZEIN OR GENISTEIN OR GLYCITEIN)
S6          2   RD (unique items)
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             UGS)
S8         66   RD (unique items)
S9         48   S8 AND (CANCER)
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dt=review
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Processing
Processed  30 of  45 files ...
Completed processing all files
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             12  DIHYDROISOFLAVONE
          98751  PRODRUG
          86862  PRODRUGS
        2735721  PRO
       15188610  DRUG
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           8607  PRO(W)DRUGS
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DIHYDROISOFLAVONE)(20n)(prodrug or prodrugs or pro()drug or pro()drugs) and
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>>>  or undefined in one or more files.
Processing
Processed  30 of  45 files ...
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           8307  ISOFLAVONOIDS
          33818  ISOFLAVONES
             12  DIHYDROISOFLAVONE
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          86862  PRODRUGS
        2735721  PRO
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        2735721  PRO
        4477753  DRUGS
           8607  PRO(W)DRUGS
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? s (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES OR
DIHYDROISOFLAVONE)(10n)(prodrug or prodrugs or pro()drug or pro()drugs)
Processing
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Processed  30 of  45 files ...
Completed processing all files
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     S12      36  (ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR
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>>>Duplicate detection is not supported for File 654.
>>>Duplicate detection is not supported for File 349.
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>>>Duplicate detection is not supported for File 391.
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>>>Duplicate detection is not supported for File 452.
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>>>Records from unsupported files will be retained in the RD set.
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     S13      21  RD (unique items)
? d s13/3/1-21
      Display 13/3/1     (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

5871883
Derwent Accession: 2004-041278
Utility
5-alkyl-7-alkylcarbonate-isoflavone ester and related method
Inventor: Roberts, William J., Gainesville, FL
Assignee: Biotest Laboratories, LLC 02), Colorado Springs, CO
Examiner: Seaman, D. Margaret (Art Unit: 165)
Assistant Examiner: Covington, Raymond
Law Firm: Sullivan Law Group

               Publication                        Application    Filing
                  Number      Kind   Date         Number         Date
              --------------  --  --------  --------------  --------
Main Patent   US 6818668       A   20041116  US 2002123068   20020412


Fulltext Word Count: 3869

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      Display 13/3/2     (Item 2 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) Format only 2005 The Dialog Corp. All rts. reserv.

0005400801
Derwent Accession: 2004-041278
5-alkyl-7-alkylcarbonate-isoflavone ester and related method
Inventor: Roberts, William, INV
Correspondence Address: SULLIVAN LAW GROUP, 1850 NORTH CENTRAL AVENUE SUITE
    1140, PHOENIX, AZ, 85004, US

               Publication                        Application    Filing
                  Number      Kind   Date         Number         Date
              --------------  --  --------  --------------  --------
Main Patent   US 20030195245  A1  20031016  US 2002123068   20020412


Fulltext Word Count: 7069

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Display 13/3/3 (Item 3 from file: 654)
DIALOG(R)File 654:US Pat.Full.

0005335699 **IMAGE Available
Derwent Accession: 2001-529661
Food product and process
Inventor: Alan Husband, INV
Graham Kelly, INV
Correspondence Address: FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP, 1300 I STREET, NW, WASHINGTON, DC, 20005, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030157225	A1	20030821	US 2002181549	20021107
PCT				WO 2001AU57	20010122
Priority				AU 20005203	20000121

Fulltext Word Count: 8827

- end of record -

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Display 13/3/4 (Item 4 from file: 654)
DIALOG(R)File 654:US Pat.Full.

0005174836 **IMAGE Available
Derwent Accession: 2003-129412
Human cDNAs and proteins and uses thereof
Inventor: Stephane Bejanin, INV
Hiroaki Tanaka, INV
Assignee: GENSET, S.A. 03), Paris, 75008, FR, 24, rue Royale
Correspondence Address: John Lucas, Ph.D., J.D. GENSET CORP., 10665 Sorrento Valley Road, San Diego, CA, 92121-1609, US

	Publication Number	Kind	Date	Application Number	Filing Date
Main Patent	US 20030027161	A1	20030206	US 2001992600	20011113
Division	PENDING			US 2001924340	20010806
Provisional				US 60-305456	20010713
Provisional				US 60-302277	20010629
Provisional				US 60-298698	20010615
Provisional				US 60-293574	20010525
Priority				WO 2001IB1715	20010806

Fulltext Word Count: 191906

- end of record -

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Display 13/3/5 (Item 1 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

01118708
AMINATED ISOFLAVONOID DERIVATIVES AND USES THEREOF
DERIVES D'ISOFLAVONOIDES AMINES ET LEURS UTILISATIONS
Patent Applicant/Assignee:
NOVOGEN RESEARCH PTY LTD, 140 Wicks Road, North Ryde, New South Wales 2113, AU, AU (Residence), AU (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
KELLY Graham Edmund, 47 Coolawin Street, Northbridge, New South Wales 2063, AU, AU (Residence), AU (Nationality), (Designated only for: US)
HEATON Andrew, 2/46-48 Abbotsford Parade, Abbotsford, New South Wales 2046, AU, AU (Residence), AU (Nationality), (Designated only for: US)
FARAGALLA Jane, 17 Manning Place, Seven Hills, New South Wales 2147, AU, AU (Residence), AU (Nationality), (Designated only for: US)
BREMNER John, 38 The Parkway, Balgownie, New South Wales 2519, AU, AU (Residence), AU (Nationality), (Designated only for: US)
Legal Representative:
HEISEY Ross Mitchell (et al) (agent), Davies Collison Cave, Level 10, 10 Barrack Street, Sydney, New South Wales 2000, AU,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200439793 A1 20040513 (WO 0439793)
Application: WO 2003AU1446 20031103 (PCT/WO AU03001446)
Priority Application: AU 2002952453 20021101
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) BW GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 12211

- end of record -

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Display 13/3/6 (Item 2 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

01057215 **Image available**
5-ALKYL-7-ALKYLCARBONATE- ISOFLAVONE **ESTER AS** ISOFLAVONE PRODRUG
ESTER DE 5-ALKYL-7-ALKYLCARBONATE-ISOFLAVONE EN TANT QUE PROMEDICAMENT A BASE D'ISOFLAVONE
Patent Applicant/Assignee:
BIOTEST LABORATORIES LLC, P.O. Box 60310, 1850 Reliable Circle, Colorado Springs, CO 80960, US, US (Residence), US (Nationality)

Inventor(s):
ROBERTS William J, 12391 S.E. 138 Avenue, Oklawaha, FL 32179, US,
Legal Representative:
SULLIVAN Stephen T (et al) (agent), Sullivan Law Group, Suite 1140, 1850 North Central Avenue, Phoenix, AZ 85004-4586, US,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200387083 A1 20031023 (WO 0387083)
Application: WO 2003US11424 20030411 (PCT/WO US0311424)
Priority Application: US 2002123068 20020412
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ
EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
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SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
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Publication Language: English
Filing Language: English
Fulltext Word Count: 5238

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Display 13/3/7 (Item 3 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

01023259
ISOFLAVONOID CONJUGATES, COMPOSITIONS THEREOF AND THERAPEUTIC METHODS INVOLVING SAME
CONJUGUES D'ISOFLAVONOIDE, COMPOSITIONS LES CONTENANT ET METHODES THERAPEUTIQUES IMPLIQUANT CEUX-CI
Patent Applicant/Assignee:
NOVOGEN RESEARCH PTY LTD, 140 Wicks Road, North Ryde, New South Wales 2113, AU, AU (Residence), AU (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
HEATON Andrew, 2/46-48 Abbotsford Parade, Abbotsford, New South Wales 2046, AU, AU (Residence), AU (Nationality), (Designated only for: US)
KELLY Graham Edmund, 47 Coolawin Street, Northbridge, New South Wales 2063, AU, AU (Residence), AU (Nationality), (Designated only for: US)
Legal Representative:
HEISEY Ross Mitchell (et al) (agent), Davies Collison Cave, Level 10, 10 Barrack Street, Sydney, New South Wales 2000, AU,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200351864 A1 20030626 (WO 0351864)
Application: WO 2002AU1722 20021219 (PCT/WO AU0201722)
Priority Application: AU 20019570 20011219
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ

EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG
SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SI SK
TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 7861

- end of record -

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Display 13/3/8 (Item 4 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

00942163
TREATMENT OF RESTENOSIS
TRAITEMENT DE LA RESTENOSE
Patent Applicant/Assignee:
NOVOGEN RESEARCH PTY LTD, 140 Wicks Road, North Ryde, New South Wales 2113, AU, AU (Residence), AU (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
HUSBAND Alan, 2/18 West Crescent Street, McMahon's Point, New South Wales 2060, AU, AU (Residence), AU (Nationality), (Designated only for: US)
KELLY Graham Edmund, 47 Coolawin Street, Northbridge, New South Wales 2063, AU, AU (Residence), AU (Nationality), (Designated only for: US)
Legal Representative:
HEISEY Ross Mitchell (et al) (agent), DAVIES COLLISON CAVE, Level 10, 10 Barrack Street, Sydney, NSW 2000, AU,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200274307 A1 20020926 (WO 0274307)
Application: WO 2002AU288 20020315 (PCT/WO AU0200288)
Priority Application: AU 20013770 20010316; AU 20015926 20010626
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ
EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR
LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI
SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 20450

- end of record -

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Display 13/3/9 (Item 5 from file: 349)

DIALOG(R)File 349:PCT FULLTEXT

00821078
FOOD PRODUCT AND PROCESS
PRODUIT ET PROCEDE ALIMENTAIRES
Patent Applicant/Assignee:
NOVOGEN RESEARCH PTY LIMITED, 140 Wicks Road, North Ryde, New South Wales 2113, AU, AU (Residence), AU (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
HUSBAND Alan James, 2/18 West Crescent Street, McMahon's Point, New South Wales 2060, AU, AU (Residence), AU (Nationality), (Designated only for: US)
KELLY Graham Edmund, 47 Coolawin Street, Northbridge, New South Wales 2063, AU, AU (Residence), AU (Nationality), (Designated only for: US)
Legal Representative:
HEISEY Ross Mitchell (et al) (agent), Davies Collison Cave, Level 10, 10 Barrack Street, Sydney, New South Wales 2000, AU,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200153285 A1 20010726 (WO 0153285)
Application: WO 2001AU57 20010122 (PCT/WO AU0100057)
Priority Application: AU 20005203 20000121
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
(OA) BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 7761

- end of record -

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Display 13/3/10 (Item 6 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

00763461 **Image available**
ADMINISTRATION OF NON-ORAL ANDROGENIC STEROIDS TO WOMEN
ADMINISTRATION DE STEROIDES ANDROGENES NON ORAUX AUX FEMMES
Patent Applicant/Assignee:
WATSON PHARMACEUTICALS INC, 311 Bonnie Circle, Corona, CA 91718, US, US (Residence), US (Nationality)
Inventor(s):
ROSARIO-JANSEN Theresa, 6773 Little River Lane, Loveland, OH 45140, US
MAZER Norman A, 4641 South Hunters Ridge Circle, Salt Lake City, UT 84124, US
Legal Representative:
WESTERN M Wayne, Thorpe, North & Western, LLP, P.O. Box 1219, Sandy, UT

84091-1219, US
Patent and Priority Information (Country, Number, Date):
Patent: WO 200076522 A1 20001221 (WO 0076522)
Application: WO 2000US15834 20000609 (PCT/WO US0015834)
Priority Application: US 99138851 19990611; US 99138854 19990611; US 99139323 19990611
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
(OA) BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English
Fulltext Word Count: 11780

- end of record -

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Display 13/3/11 (Item 7 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
(c) 2005 WIPO/Univentio. All rts. reserv.

00753411 **Image available**
ISOFLAVONE METABOLITES
METABOLITES D'ISOFLAVONE
Patent Applicant/Assignee:
G J CONSULTANTS PTY LTD, 21 Kooloona Crescent, West Pymble, NSW 2073, AU, AU (Residence), AU (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
JOANNOU George Eustace, 21 Kooloona Crescent, West Pymble, NSW 2073, AU, AU (Residence), AU (Nationality), (Designated only for: US)
Legal Representative:
SPRUSON & FERGUSON, GPO Box 3898, Sydney, NSW 2001, AU
Patent and Priority Information (Country, Number, Date):
Patent: WO 200066576 A1 20001109 (WO 0066576)
Application: WO 2000AU392 20000501 (PCT/WO AU0000392)
Priority Application: AU 9982 19990430
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
(EP) AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
(OA) BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
(AP) GH GM KE LS MW SD SL SZ TZ UG ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Publication Language: English
Filing Language: English

Applicant

Fulltext Word Count: 12232

- end of record -

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Display 13/3/12 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

16392292 Document Delivery Available: 000183613000014 References: 28
TITLE: Identification of CYP1A2 as the main isoform for the phase I hydroxylated metabolism of genistein and a prodrug **converting enzyme of methylated** isoflavones
AUTHOR(S): Hu M (REPRINT); Krausz K; Chen J; Ge X; Li JQ; Gelboin HL; Gonzalez FJ
AUTHOR(S) E-MAIL: minghu@wsu.edu
CORPORATE SOURCE: Washington State Univ, Dept Pharmaceut Sci, /Pullman//WA/99164 (REPRINT); Washington State Univ, Dept Pharmaceut Sci, /Pullman//WA/99164; NCI, NIH, /Bethesda//MD/20892; NCI, NIH, /Bethesda//MD/20892; Shanghai Inst Pharmaceut Ind, Dept Med Chem, /Shanghai//Peoples R China/
PUBLICATION TYPE: JOURNAL
PUBLICATION: DRUG METABOLISM AND DISPOSITION, 2003, V31, N7 (JUL), P924-931
GENUINE ARTICLE#: 691NU
PUBLISHER: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA
ISSN: 0090-9556
LANGUAGE: English DOCUMENT TYPE: ARTICLE (ABSTRACT AVAILABLE)

- end of record -

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Display 13/3/13 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01672908
5-ALKYL-7-ALKYLCARBONATE- ISOFLAVONE **ESTER AS** ISOFLAVONE PRODRUG
ESTER DE 5-ALKYL-7-ALKYLCARBONATE-ISOFLAVONE EN TANT QUE PROMEDICAMENT A BASE D'ISOFLAVONE
PATENT ASSIGNEE:
Biotest Laboratories, LLC, (4581490), P.O. Box 60310, 1850 Reliable Circle, Colorado Springs, CO 80960, (US), (Applicant designated States: all)
INVENTOR:
ROBERTS, William, J., 12391 S.E. 138 Avenue, Oklawaha, FL 32179, (US)
PATENT (CC, No, Kind, Date):
WO 2003087083 031023
APPLICATION (CC, No, Date): EP 2003746754 030411; WO 2003US11424 030411
PRIORITY (CC, No, Date): US 123068 020412
DESIGNATED STATES: AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HU; IE; IT; LI; LU; MC; NL
EXTENDED DESIGNATED STATES: AL; LT; LV; MK
INTERNATIONAL PATENT CLASS: C07D-311/36; A61K-031/35; A61P-021/06
LANGUAGE (Publication,Procedural,Application): English; English; English

- end of record -

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Display 13/3/14 (Item 1 from file: 340)
DIALOG(R)File 340:CLAIMS(R)/US Patent

04158506 2004-0037249
C/(A1) 5-ALKYL-7-ALKYLCARBONATE-ISOFLAVONE ESTER AND RELATED METHOD; ADMINISTERING PRODRUGS **OF METABOLITES SUCH AS 5-METHYL-7-ETHYL CARBONATE-** ISOFLAVONE **, TO INCREASING CONCENTRATION OF FLAVONOIDS (B2) 5-ALKYL-7-ALKYLCARBONATE-ISOFLAVONE ESTER AND RELATED METHOD**
Inventors: Roberts William J (US)
Assignee: (A1) Unassigned Or Assigned To Individual
(B2) Biotest Laboratories LLC
Assignee Code: (A1) 68000; (B2) 66791

	Publication Number	Kind	Date	Application Number	Date
	US 20030195245	A1	20031016	US 2002123068	20020412
	US 6818668	B2	20041116	US 2002123068	20020412
Prior Publication:	US 20030195245	A1	20031016		
Priority Applic:				US 2002123068	20020412

Calculated Expiration: 20220412

- end of record -

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Display 13/3/15 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10842072 Genuine Article#: 564CE No. References: 0
Title: Isoflavone prodrugs **as glioblastoma inhibitors**
Author(s): Bhushan A; Lynch L; Adejare A
Corporate Source: Idaho State Univ,Coll Pharm, Dept Pharmaceut Sci,Pocatello//ID/83209
Journal: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, 2002, V223, 2 (APR 7), PB132-B132
ISSN: 0065-7727 Publication date: 20020407
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA
Language: English Document Type: MEETING ABSTRACT

- end of record -

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Display 13/3/16 (Item 1 from file: 148)
DIALOG(R)File 148:Gale Group Trade & Industry DB

0016992554 SUPPLIER NUMBER: 116439214 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Vyrex Corporation Announces Launch of Its New Website.
Business Wire, 5067
May 11, 2004
LANGUAGE: English RECORD TYPE: Fulltext
WORD COUNT: 508 LINE COUNT: 00051

- end of record -

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Display 13/3/17 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

16278114 PASCAL No.: 03-0441284
Identification of CYP1A2 as the main isoform for the phase I hydroxylated metabolism of genistein and A prodrug **converting enzyme of methylated** isoflavones
MING HU; KRAUSZ Kristopher; JUN CHEN; XIA GE; JIANQI LI; GELBOIN Harry L; GONZALEZ Frank J
Laboratory of Molecular Carcinogenesis, National Cancer Institute, National Institute of Health, Bethesda, Maryland, United States; Laboratory of Metabolism, National Cancer Institute, National Institute of Health, Bethesda, Maryland, United States; Department of Pharmaceutical Sciences, College of Pharmacy, Washington State University, Pullman, Washington, United States; Department of Medicinal Chemistry, Shanghai Institute of Pharmaceutical Industries, Shanghai, China
Journal: Drug metabolism and disposition, 2003, 31 (7) 924-931
Language: English

- end of record -

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Display 13/3/18 (Item 1 from file: 484)
DIALOG(R)File 484:Periodical Abs Plustext

05030542 SUPPLIER NUMBER: 71514165 (USE FORMAT 7 OR 9 FOR FULLTEXT)
Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements
Setchell, Kenneth D R; Brown, Nadine M; Desai, Pankaj; Zimmer-Nechemias, Linda; Et al
Journal of Nutrition (IJNU), v131 n4S, pS1362-S1375, p.14
Apr 2001
ISSN: 0022-3166 JOURNAL CODE: IJNU
DOCUMENT TYPE: Feature
LANGUAGE: English RECORD TYPE: Fulltext; Abstract
WORD COUNT: 10845

- end of record -

?

Display 13/3/19 (Item 1 from file: 35)
DIALOG(R)File 35:Dissertation Abs Online

01938755 ORDER NO: AADAA-I3083903
Isoflavones and their novel analogues: Effects on EGFR and PTEN/AKT-mediated signaling pathways in glioblastoma multiforme cells
Author: Lynch, Launa M. J.
Degree: Ph.D.

```
  Year:    2003
  Corporate Source/Institution:  Idaho State University (0320)
  Source:  VOLUME 64/03-B OF DISSERTATION ABSTRACTS INTERNATIONAL.
           PAGE 1199.  159 PAGES

                                - end of record -
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     Display 13/3/20     (Item 1 from file: 345)
DIALOG(R)File 345:Inpadoc/Fam.& Legal Stat
(c) 2005 EPO. All rts. reserv.

19352160
Basic Patent (No,Kind,Date): US 20030195245 AA 20031016   <No. of Patents:
003>
  5-alkyl-7-alkylcarbonate-isoflavone ester and related method (English)
Patent Assignee: ROBERTS WILLIAM J (US)
Author (Inventor): ROBERTS WILLIAM J (US)
National Class: *514456000; 549406000
IPC: *A61K-031/353; C07D-311/76
Derwent WPI Acc No: C 04-041278
Language of Document: English
Patent Family:
    Patent No    Kind  Date      Applic No   Kind  Date
    US 20030195245  AA  20031016    US 123068       A   20020412  (BASIC)
    US 6818668      BB  20041116    US 123068       A   20020412
    WO 200387083    A1  20031023    WO 2003US11424  A   20030411
Priority Data (No,Kind,Date):
    US 123068 A  20020412

                                - end of record -
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     Display 13/3/21     (Item 1 from file: 452)
DIALOG(R)File 452:Drug Data Report
(c) 2005 Prous Science. All rts. reserv.

00284427       (Structure Image Available)
GENERIC NAME   Genistein-7-phosphate
CHEM NAME:     Phosphoric acid 5-hydroxy-3-(4-hydroxyphenyl)-4-oxo-4H-1-ben
               zopyran- 7-yl monoester
FORMULA:       C15H11O8P
DEVEL. PHASE:  Biological Testing
ORIGINATOR:    Vyrex
CLASS:         50050  (Treatment of Osteoporosis)
               75000  (Oncolytic Drugs)
RELATED ENTRY: 122175 (non-specific)
PREV. PUB. IN: Drug Data Report, Vol. 22, No. 2, p. 187, 2000

                                - end of record -
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? d s13/7/6,7,12,13,15
>>>Format 7 is not valid in file 759
>>>Format 7 is not valid in file 761
     Display 13/7/6     (Item 2 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT
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01057215 **Image available**

5-ALKYL-7-ALKYLCARBONATE- ISOFLAVONE **ESTER AS** ISOFLAVONE PRODRUG

ESTER DE 5-ALKYL-7-ALKYLCARBONATE-ISOFLAVONE EN TANT QUE PROMEDICAMENT A BASE D'ISOFLAVONE

Patent Applicant/Assignee:
BIOTEST LABORATORIES LLC, P.O. Box 60310, 1850 Reliable Circle, Colorado Springs, CO 80960, US, US (Residence), US (Nationality)
Inventor(s):
ROBERTS William J, 12391 S.E. 138 Avenue, Oklawaha, FL 32179, US,
Legal Representative:
SULLIVAN Stephen T (et al) (agent), Sullivan Law Group, Suite 1140, 1850 North Central Avenue, Phoenix, AZ 85004-4586, US,

Patent and Priority Information (Country, Number, Date):
Patent: WO 200387083 A1 20031023 (WO 0387083)
Application: WO 2003US11424 20030411 (PCT/WO US0311424)
Priority Application: US 2002123068 20020412
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Main International Patent Class: C07D-311/36
International Patent Class: A61K-031/35; A61P-021/06
Publication Language: English
Filing Language: English
Fulltext Word Count: 5238

English Abstract
A compound is provided for increasing the concentration of a parent isoflavone in a subject in vivo. The parent isoflavone has a skeletal structure including a 5 position and a 7 position, a 5 alkyl group, and a 7-hydroxy grouo with a 7-hydroxy oxygen appended to the 7 position and a 7-hydroxy hydrogen appended to the 7-hydroxy oxygen. The compound includes a substrate having the skeletal structure of the parent isoflavone, with a 5 position and a 7 position corresponding to the 5 and 7 positions respectively of the parent isoflavone. An alkyl group is appended to the 5 position. A promoiety is appended to the 7-hydroxy oxygen of the substrate as a substitute fir the 7-hydroxy hydrogen of the parent isoflavone, the promoiety and the 7-hydroxy oxygen establishing an alkylcarbonate ester including an alkyl group having at least three carbon atoms. Wherein R"sup"1 consists of a member selected from the group consisting of a straight- chain, branched, and cyclic alkyl comprising at least three carbon atoms; R"sup"2 consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl; R"sup"3 and R"sup"4 are the same or different, and selected from the group consisting of hydrogen, alkyl, hydroxy, and alkyoxy; and R"sup"5 consists of a member selected from the group consisting of hydrogen and an alkyl.

French Abstract
L'invention concerne un compose permettant d'augmenter in vivo chez un sujet la concentration d'isoflavone parente, laquelle a une structure squelette a position 5 et position 7, groupe alkyle, et groupe 7-hydroxy, avec 7-hydroxy oxygene ajoute en position 7 et 7-hydroxy hydrogene ajoute en 7-hydroxy oxygene. Ce compose comprend un substrat ayant la structure squelette de l'isoflavone parente, avec des positions 5 et 7 correspondant respectivement aux positions 5 et 7 de l'isoflavone parente. Un groupe alkyle est ajoute en position 5. Un groupe fonctionnel promoteur est ajoute en 7-hydroxy oxygene du substrat, se substituant au 7-hydroxy hydrogene de l'isoflavone parente, le groupe fonctionnel promoteur et 7-hydroxy oxygene etablissant un ester d'alkylcarbonate a groupe alkyle ayant au moins trois atomes de carbone, selon la formule ci-apres. Dans cette formule, R"sup"1 appartient au groupe constitue par alkyle a chaine droite, chaine ramifiee et cyclique comprenant au moins trois atomes de carbone; R"sup"2 appartient au groupe constitue par alkyle a chaine droite, chaine ramifiee et cyclique; R"sup"3 et R"sup"4, identiques ou differents, appartiennent au groupe constitue par hydrogene, alkyle, hydroxy, et alkyoxy; et R"sup"5 appartient au groupe constitue par hydrogene et alkyle.

Legal Status (Type, Date, Text)
Publication 20031023 A1 With international search report.
Examination 20031224 Request for preliminary examination prior to end of 19th month from priority date

Claim

1 A compound comprising an alkylearbonate ester, the compound represented by the formula

R2 0 R4

R3

RIOC(O)

R5

wherein

RI consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl comprising at least three carbon atoms;

R2 consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl;

R3 and R4 are the same or different, and selected from the group consisting of hydrogen, alkyl, hydroxy, and alkyoxy; and

R5 consists of a member selected from the group consisting of hydrogen and an alkyl.

2 A compound as set forth in claim 1, wherein RI has 4 to 22 carbon atoms.

3 A compound as set forth in claim 2, wherein the alkylcarbonate ester consists of a member selected from the group consisting of butyl carbonate, isobutyl carbonate, t-butyl carbonate, valeryl carbonate, hexyl carbonate, heptyl carbonate, octyl carbonate, nonyl carbonate, decyl carbonate, undecyl carbonate, dodecyl carbonate, cyclopentyl methyl carbonate, cyclopentylpropyl carbonate, cyclohexyl methyl carbonate, and cyclohexylpropyl carbonate.

14
. A compound as set forth in claim 1, wherein RI has 14 to 22 carbon atoms.

5 A compound as set forth in claim 1, wherein RI has 16 to 22 carbon atoms.

6 A compound as set forth in claim 1, wherein RI comprises a stearyl group.

7 A compound as set forth in claim 1, wherein R2 consists of methyl.

8 A compound comprising an alkylcarbonate ester, the compound represented by the formula
R2 0
RIOC(O)o
wherein
RI consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl comprising at least three carbon
atoms; and
R2 consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl.

9 A compound as set forth in claim 8, wherein RI has 4 to 22 carbon atoms.

10 A compound as set forth in claim 9, wherein the alkylearbonate ester consists of a member selected from the group consisting of butyl carbonate, isobutyl carbonate, t-butyl carbonate, valeryl carbonate, hexyl
carbonate, heptyl carbonate, octyl carbonate, nonyl carbonate, decyl carbonate, undecyl carbonate, dodecyl carbonate, cyclopentyl methyl
15
carbonate, cyclopentylpropyl carbonate, cyclohexyl methyl carbonate, and cyclohexylpropyl carbonate.
11 A compound as set forth in claim 8, wherein RI has 14 to 22 carbon atoms.

12 A compound as set forth in claim 8, wherein RI has 16 to 22 carbon atoms.

13 A compound as set forth in claim 8, wherein RI comprises a stearyl group.

14 A compound as set forth in claim 8, wherein R2 Consists Of methyl.

15 A compound for increasing the concentration of a parent isoflavone in a sub'ect in vivo, the parent isoflavone having a skeletal structure including a 5 position and a 7 position and the parent isoflavone further having a 5 alkyl group and a 7-hydroxy group comprising a 7-hydroxy oxygen appended to the 7 position and a 7-hydroxy hydrogen appended to the
7-hydroxy oxygen, the compound comprising:
a substrate having the skeletal structure of the parent isoflavone, the

substrate comprising a 5 position and a 7 position corresponding to the 5 and
7 positions respectively of the parent isoflavone;
a substituent selected from the group consisting of a straight-chain, branched, and cyclic alkyl appended to the 5 position; and
a promoiety appended to the 7-hydroxy oxygen of the substrate as a substitute for the 7-hydroxy hydrogen of the parent isoflavone, the promoiety and the 7-hydroxy oxygen establishing an alkylcarbonate ester comprising an
alkyl group comprising at least three carbon atoms.

16 A compound as set forth in claim 15, wherein the alkyl group of the alkylcarbonate ester has 4 to 22 carbon atoms.

17 A compound as set forth in claim 15, wherein the alkylcarbonate ester consists of a member selected from the group consisting of propyl
16
carbonate, isopropyl carbonate, butyl carbonate, isobutyl carbonate, t-butyl
carbonate, valeryl carbonate, hexyl carbonate, heptyl carbonate, octyl carbonate, nonyl carbonate, decyl carbonate, undecyl carbonate, dodecyl carbonate, cyclopentyl methyl carbonate, cyclopentylpropyl carbonate, cyclohexyl methyl carbonate, and cyclohexylpropyl carbonate.
18 A compound as set forth in claim 15, wherein the alkyl group of the alkylearbonate ester has 14 to 22 carbon atoms.

19 A compound as set forth in claim 15, wherein the alkyl group of the alkylcarbonate ester has 14 to 22 carbon atoms.

20 A compound as set forth in claim 15, wherein the substituent appended to the 5 position is methyl.

21 A compound as set forth in claim 15, wherein alkyl group of the alkylcarbonate ester comprises a stearyl group.

22 A method for increasing the concentration of a parent isoflavone in a subject in vivo, the parent isoflavone having a skeletal structure , including a 5 position and a 7 position and the parent isoflavone further having a 5 alkyl group and a 7-hydroxy group comprising a 7-hydroxy oxygen appended to the 7 position and a 7-hydroxy hydrogen appended to the 7
hydroxy oxygen, the method comprising:
administering to the sub'ect a compound comprising formula I, and
converting the compound in vivo into the parent I'Lsoflavone,
wherein formula I is represented by
-D
0
2 5
R3
R10C(O)
R5
17
wherein
R1 consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl comprising at least three carbon
atoms;

R2 Consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl;
R3 and R4 are the same or different, and selected from the group consisting of hydrogen, alkyl, hydroxy, and alkyoxy; and
R5 consists of a member selected from the group consisting of hydrogen and an alkyl.

23 A method as set forth in claim 22, wherein R1 has 4 to 22 carbon atoms.
24 A method as set forth in claim 23, wherein the alkylcarbonate ester consists of a member selected from the group consisting of butyl carbonate, isobutyl carbonate, t-butyl carbonate, valeryl carbonate, hexyl
carbonate, heptyl carbonate, octyl carbonate, nonyl carbonate, decyl carbonate, undecyl carbonate, dodecyl carbonate, cyclopentyl methyl carbonate, cyclopentylpropyl carbonate, cyclohexyl methyl carbonate, and cyclohexylpropyl carbonate.

25 A method as set forth in claim 22, wherein R1 has 14 to 22 carbon atoms.

26 A method as set forth in claim 22, wherein R1 has 16 to 22 carbon atoms.

27 A method as set forth in claim 22, wherein RI comprises a stearyl group.

28 A method as set forth in claim 22, wherein R2 consists of methyl.

29 A method for increasing the concentration of a parent isoflavone in a subject in vivo, the parent isoflavone having a skeletal structure including a 5 position and a 7 position and the parent isoflavone further 18
having a 5 alkyl group and a 7-hydroxy group comprising a 7-hydroxy oxygen appended to the 7 position and a 7-hydroxy hydrogen appended to the 7
hydroxy oxygen, the method comprising:
administering to the subject a compound comprising formula I, and converting the compound in vivo into the parent isoflavone,
wherein formula I is represented by
R2 0
RIOC(0)0
wherein
RI consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl comprising at least three carbon
atoms; and
R2 consists of a member selected from the group consisting of a straight-chain, branched, and cyclic alkyl.

30 A method as set forth in claim 29, wherein RI has 4 to 22 carbon atoms.
31 A method as set forth in claim 30, wherein the alkylcarbonate ester consists of a member selected from the group consisting of butyl carbonate, isobutyl carbonate, t-butyl carbonate, valeryl carbonate, hexyl
carbonate, heptyl carbonate, octyl carbonate, nonyl carbonate, decyl

carbonate, undecyl carbonate, dodecyl carbonate, cyclopentyi methyl carbonate, cyclopentylpropyl carbonate, cyclohexyl methyl carbonate, and cyclohexylpropyl carbonate.

19
. A method as set forth in claim 29, wherein R1 has 14 to 22 carbon atoms.

33 A method as set forth in claim 29, wherein R1 has 16 to 22 carbon atoms.

34 A method as set forth in claim 29, wherein R1 comprises a stearyl group.

35 A method as set forth in claim 29, wherein R2 consists of methyl.

36 A method for increasing the concentration of a parent isoflavone in a sub'ect in vivo, the parent isoflavone having a skeletal structure including a 5 position and a 7 position and the parent isoflavone further having a 5 alkyl group and a 7-hydroxy group comprising a 7-hydroxy oxygen appended to the 7 position and a 7-hydroxy hydrogen appended to the 7
hydroxy oxygen, the method comprising:
administering to the subject a compound comprising a substrate and a 1 5 promoiety, the substrate having the skeletal structure of the parent isoflavone, the substrate comprising a 5 position and a 7 position corresponding to the 5 and 7 positions respectively of the parent isoflavone, the 5 position having an alkyl group appended thereto, the promoiety being appended to the 7-hydroxy oxygen of the substrate as a substitute for the 7hydroxy hydrogen of the parent isoflavone, the promoiety and the 7-hydroxy
oxygen establishing an alkylearbonate ester comprising an alkyl group comprising at least 3 carbon atoms; and
converting the compound in vivo into the parent I'Lsoflavone.

37 A method as set forth in claim 36, wherein the alkyl group of the alkylearbonate ester has 4 to 22 carbon atoms.

38 A method as set forth in claim 36, wherein the alkylcarbonate ester consists of a member selected from the group consisting of propyl carbonate, isopropyl carbonate, butyl carbonate, isobutyl carbonate, t-butyl
carbonate, valeryl carbonate, hexyl carbonate, heptyl carbonate, octyl
20
carbonate, nonyl carbonate, decyl carbonate, undecyl carbonate, dodecyl carbonate, cyclopentyl methyl carbonate, cyclopentylpropyl carbonate, cyclohexyl methyl carbonate, and cyclohexylpropyl carbonate.

39 A method as set forth in claim 36, wherein the alkyl group of the alkylcarbonate ester has 14 to 22 carbon atoms.

40 A method as set forth in claim 36, wherein the alkyl group of the alkylcarbonate ester has 16 to 22 carbon atoms.

41 A method as set forth in claim 36, wherein the substituent appended to the 5 position is methyl.

42 A method as set forth in claim 36, wherein the alkyl group of the

alkylcarbonate ester comprises a stearyl group.
21

- end of record -

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Display 13/7/7 (Item 3 from file: 349)
DIALOG(R)File 349:PCT FULLTEXT

01023259
ISOFLAVONOID CONJUGATES, COMPOSITIONS THEREOF AND THERAPEUTIC METHODS INVOLVING SAME
CONJUGUES D'ISOFLAVONOIDE, COMPOSITIONS LES CONTENANT ET METHODES THERAPEUTIQUES IMPLIQUANT CEUX-CI
Patent Applicant/Assignee:
NOVOGEN RESEARCH PTY LTD, 140 Wicks Road, North Ryde, New South Wales 2113, AU, AU (Residence), AU (Nationality), (For all designated states except: US)
Patent Applicant/Inventor:
HEATON Andrew, 2/46-48 Abbotsford Parade, Abbotsford, New South Wales 2046, AU, AU (Residence), AU (Nationality), (Designated only for: US)
KELLY Graham Edmund, 47 Coolawin Street, Northbridge, New South Wales 2063, AU, AU (Residence), AU (Nationality), (Designated only for: US)
Legal Representative:
HEISEY Ross Mitchell (et al) (agent), Davies Collison Cave, Level 10, 10 Barrack Street, Sydney, New South Wales 2000, AU,
Patent and Priority Information (Country, Number, Date):
Patent: WO 200351864 A1 20030626 (WO 0351864)
Application: WO 2002AU1722 20021219 (PCT/WO AU0201722)
Priority Application: AU 20019570 20011219
Designated States:
(Protection type is "patent" unless otherwise stated - for applications prior to 2004)
AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
(EP) AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SI SK TR
(OA) BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG
(AP) GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW
(EA) AM AZ BY KG KZ MD RU TJ TM
Main International Patent Class: C07D-311/38
International Patent Class: C07D-311/58; C07C-305/24; C07H-015/26; A61K-031/255; A61K-031/352; A61K-031/353; A61K-031/7048; A61P-017/00; A61P-019/02; A61P-025/00; A61P-035/00; A61P-037/00
Publication Language: English
Filing Language: English
Fulltext Word Count: 7861

English Abstract
The invention relates to compounds, formulations, drinks, foodstuffs, methods and therapeutic uses involving, containing, comprising, including and/or for preparing isoflavone conjugate compounds and analogues thereof. More preferably the invention relates to sulfoconjugates and glucoconjugates of isoflavonoids, medicaments involving same and

therapeutic uses thereof.

French Abstract

L'invention concerne des composes, des formulations, des boissons, des produits alimentaires, des methodes et des utilisations therapeutiques impliquant, contenant, comprenant, possedant des composes de conjugue d'isoflavone et des composes identiques a ceux-ci; et/ou des methodes de preparation de ceux-ci. L'invention concerne plus particulierement des sulfoconjugues et des glucoconjugues d'isoflavonoides, des medicaments impliquant ceux-ci et des utilisations therapeutiques de ceux-ci.

Legal Status (Type, Date, Text)
Publication 20030626 A1 With international search report.
Examination 20030731 Request for preliminary examination prior to end of 19th month from priority date

Claim

1 An isoflavonoid conjugate of the general formula I:
W
R, A
z B
R2
in which
RI, R2 and Z are independently SO20k an O-sugar residue, hydrogen, hydroxy,
OR9, OC(O)Rlo3 OS(O)RIo, CHO@ QO)Rio@ COOH5 C02R,o@ CONR3R49 alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, alkoxyaryl, thio,
alkylthio, amino, alkylamino, dialkylamino, nitro or halo, or
R2 is as previously defined, and RI and Z taken together with the carbon atoms to which
they are attached form a five-membered ring selected from
0 0
T%X or
0==<
T 0 0
RI is as previously defined, and R2 and Z taken together with the carbon atoms to which
they are attached form a five-membered ring selected ftom
0 @O
TA@ 0 0
T
and
W is RI, A is SO20H, an O-sugar residue, hydrogen, hydroxy, NR31ZA or thio, and B
is selected from
- 31
R R6 R5
or
Y Y
0 0
W is R1, and A and B taken together with the carbon atoms to which they are attached
form a six-membered ring selected from
X R6 X R6 X R6
Y Y Y
R7 R7 or

X R6 X R6
Y Y
OR7
W, A and B taken together with the groups to which they are associated comprise
R8 R8 R8
RI R6 RI R6 RI R6
or
z Y z Y z Y
R2 0 R2 0 R2 0
W and A taken together with the groups to which they are associated comprise
R8 R8 R8
RI RIO RI RIO RI RIO
z B
z B z B
R2 R2
and B is
- 32
R5 R5 R5
Y Y
0 0 0
wherein
R3 is hydrogen, alkyl, aryl, arylalkyl, an amino acid, C(O)Rji where RI, is hydrogen alkyl, aryl, arylalkyl or an amino acid, or C02RI2 where R12 is hydrogen, alkyl,
haloalkyl, aryl, heteroaryl or arylalkyl,
R4 is hydrogen, alkyl or aryl,
or R3 and R4 taken together with the nitrogen to which they are attached comprise
pyrrolidinyl or piperidinyl,
Rs is SO20H, an O-sugar residue, hydrogen, C(O)Rj 1 where RI 1 is as previously
defined, or C02RI2 where R12 is as previously defined,
R6 is SO20H, an O-sugar residue, hydrogen, hydroxy, alkyl, aryl, amino, thio, NR3R4,CORII where RI, is as previously defined, C02RI2 where R12 is as previously
defined or CONR3R4,
R7 is hydrogen, C(O)RI 1 where RI I is as previously defined, alkyl, haloalkyl, aryl, arylalkyl or Si(R13)3 where each R13 is independently hydrogen, alkyl or aryl,
Rg is SO20H, an O-sugar residue, hydrogen, hydroxy, alkoxy or alkyl,
R9 is alkyl, haloalkyl, aryl, arylalkyl, C(O)Rj 1 where RI 1 is as previously defined, or
Si(RI3)3 where R13 is as previously defined,
Rio is hydrogen, alkyl, haloalkyl, amino, aryl, arylalkyl, an amino acid, alkylamino or
dialkylamino,
the drawing "=" represents either a single bond or a double bond,
T is independently hydrogen, alkyl or aryl,
* is 0, NR4 or S, preferably 0, and
* is
R16
R15 R14
wherein
R14, R15 and R16 are independently SO20H, an O-sugar residue, hydrogen, hydroxy,

OR9@ OC(O)RIO, OS(O)Rio@ CH03 C(O)Rio@ COOH@ C02R,o, CONR3R4, alkyl, haloalkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, alkylaryl, alkoxyaryl, thio,
alkylthio, amino, alkylamino, dialkylainino, nitro or halo, and
wherein at least one of RI, R23 R5@ R6@ R85 R14, R15, R16, Z, W or A where present is
independently SO20H or an O-sugar residue,
or a pharmaceutically acceptable salt or **prodrug** thereof

2 An **isoflavonoid** conjugate of claim 1. wherein the sulfoconjugate moiety is present as a corresponding salt SO20M, where M is a pharmaceutically acceptable cation. 3 . An isoflavonoid conjugate of claim 1, wherein the sugar residue is selected from the group consisting of natural sugars, modified sugars, and mono-, di- and polysaccharides.

4 An isoflavonoid conjugate of claim 3, wherein the sugar residue is selected from the group consisting of glucose, altrose, mannose, galactose, fiUctose, talose, xylose, arabinose, ribose, sorbose, sucrose, lactose and maltose.

5 An isoflavonoid conjugate of claim 4. wherein the sugar residue is selected from the group consisting of 0,D-glucoside, malonyl glucoside, acetyl glucoside and 0,Dglucuronide.

6 A method for the treatment, prophylaxis, amelioration, defence against, and/or prevention of one or more of the therapeutic indications as hereinbefore defined, which - 34 comprises administering to a subj'ect a therapeutically effective amount of one or more compounds of formula I as defined in claim 1.

7 Use of one or more compounds of formula I for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of one or more of the therapeutic indications as hereinbefore described.

8 An agent for the treatment, prophylaxis, amelioration, defence against and/or treatment of one or more of the therapeutic indications as hereinbefore defined which comprises one or more compounds of formula I either alone or in association with one or more carriers or excipients.

9 A method for the treatment, prophylaxis, amelioration, defence against and/or prevention of conditions in a subject associated with abnormal estrogen/androgen balance.

10 A method of claim 9, wherein the subject is a woman.

11 A method of claim 9, wherein the subject is a man.

12 Use of one or more compounds of formula I for the manufacture of a medicament for the treatment, amelioration, defence against, prophylaxis and/or prevention of conditions in a subject associated with abnormal estrogen/androgen balance.

13 A therapeutic composition which comprises one or more compounds of formula I in association with one or more pharmaceutical carriers and/or excipients.

14 A drink or food-stuff, which contains one or more compounds of formula I.

15 A composition comprising one or more compounds of formula I, vitamin E, and optionally pharmaceutically, veterinarily or cosmetically acceptable carriers and/or excipients.

- end of record -

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Display 13/7/12 (Item 1 from file: 440)

16392292 Document Delivery Available: 000183613000014 References: 28

TITLE: Identification of CYP1A2 as the main isoform for the phase I hydroxylated metabolism of genistein and a prodrug **converting enzyme of methylated** isoflavones

AUTHOR(S): Hu M (REPRINT); Krausz K; Chen J; Ge X; Li JQ; Gelboin HL; Gonzalez FJ
AUTHOR(S) E-MAIL: minghu@wsu.edu
CORPORATE SOURCE: Washington State Univ, Dept Pharmaceut Sci, /Pullman//WA/99164 (REPRINT); Washington State Univ, Dept Pharmaceut Sci, /Pullman//WA/99164; NCI, NIH, /Bethesda//MD/20892; NCI, NIH, /Bethesda//MD/20892; Shanghai Inst Pharmaceut Ind, Dept Med Chem, /Shanghai//Peoples R China/

PUBLICATION TYPE: JOURNAL
PUBLICATION: DRUG METABOLISM AND DISPOSITION, 2003, V31, N7 (JUL), P924-931
GENUINE ARTICLE#: 691NU
PUBLISHER: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA
ISSN: 0090-9556
CURRENT CONTENTS JOURNAL ANNOUNCEMENT: CC LIFE, V46, N142
LANGUAGE: English DOCUMENT TYPE: ARTICLE
SUBFILE: CC LIFE--Current Contents/Life Sciences

ABSTRACT: This study determined the cytochrome P450 (P450) isoforms responsible for metabolism of isoflavones using human liver microsomes (HLM) and expressed P450s. The primary metabolite of genistein is 3'-OH-genistein, as identified with an authentic chemically synthesized standard. CYP1A2 was predominantly responsible for 3'-OH-genistein formation since its formation was inhibited (>50%, $p < 0.05$) by a monoclonal antibody specific for CYP1A2, was correlated with CYP1A2 activities of HLM, and was catalyzed by expressed CYP1A2. In addition to CYP1A2, CYP2E1 also catalyzed, although to a lesser extent, its formation. The contribution of these P450s to the formation of 3'-OH-genistein was also confirmed with a panel of expressed enzymes. Methylated isoflavones biochanin A, prunetin, and formononetin (10-100 μM) were rapidly converted by HLM and expressed CYP1A2 to more active genistein and daidzein. The conversion of biochanin A to genistein appears to be mainly mediated by CYP1A2 because of the strong correlation between the conversion rates and CYP1A2 activities in HLM. Thus, CYP1A2 is an effective **prodrug** -converting enzyme for less active methylated **isoflavones** . CYP1A2-catalyzed conversion of biochanin A to genistein (K-m, 7.80 μM; V-max, 903 pmol/min/mg of protein; V-max/K-m, 116 μl/min/mg of protein) was much faster than 3'-hydroxylation of genistein (K-m, 12.7 μM and V-max, 109 pmol/min/mg of protein; V-max/K-m, 8.6 μl/min/mg of protein).

The interaction studies showed that genistein inhibited formation of acetaminophen from phenacetin with an IC50 value of 16 µM. Additional studies showed that phenacetin and genistein were mutually inhibitory. In conclusion, CYP1A2 and CYP2E1 metabolized genistein and CYP1A2 acted as **prodrug** -converting enzymes for other less active methylated **isoflavones** .

- end of record -

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Display 13/7/13 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS
(c) 2005 European Patent Office. All rts. reserv.

01672908
5-ALKYL-7-ALKYLCARBONATE- ISOFLAVONE **ESTER AS** ISOFLAVONE PRODRUG
ESTER DE 5-ALKYL-7-ALKYLCARBONATE-ISOFLAVONE EN TANT QUE PROMEDICAMENT A BASE D'ISOFLAVONE
PATENT ASSIGNEE:
Biotest Laboratories, LLC, (4581490), P.O. Box 60310, 1850 Reliable Circle, Colorado Springs, CO 80960, (US), (Applicant designated States: all)
INVENTOR:
ROBERTS, William, J., 12391 S.E. 138 Avenue, Oklawaha, FL 32179, (US)
PATENT (CC, No, Kind, Date): WO 2003087083 031023
APPLICATION (CC, No, Date): EP 2003746754 030411; WO 2003US11424 030411
PRIORITY (CC, No, Date): US 123068 020412
DESIGNATED STATES: AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HU; IE; IT; LI; LU; MC; NL
EXTENDED DESIGNATED STATES: AL; LT; LV; MK
INTERNATIONAL PATENT CLASS: C07D-311/36; A61K-031/35; A61P-021/06
LEGAL STATUS (Type, Pub Date, Kind, Text):
Application: 031217 A1 International application. (Art. 158(1))
Application: 031217 A1 International application entering European phase
LANGUAGE (Publication,Procedural,Application): English; English; English

- end of record -

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Display 13/7/15 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2005 Inst for Sci Info. All rts. reserv.

10842072 Genuine Article#: 564CE Number of References: 0
Title: Isoflavone prodrugs **as glioblastoma inhibitors**
Author(s): Bhushan A; Lynch L; Adejare A
Corporate Source: Idaho State Univ,Coll Pharm, Dept Pharmaceut Sci,Pocatello//ID/83209
Journal: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, 2002, V223, 2 (APR 7), PB132-B132
ISSN: 0065-7727 Publication date: 20020407
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA
Language: English Document Type: MEETING ABSTRACT

- end of record -

? d s13/9/15

Display 13/9/15 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10842072 Genuine Article#: 564CE Number of References: 0
Title: Isoflavone prodrugs **as glioblastoma inhibitors**
Author(s): Bhushan A; Lynch L; Adejare A
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ISSN: 0065-7727 Publication date: 20020407
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA
Language: English Document Type: MEETING ABSTRACT
Meeting Abstract Number: 203-MEDI
Geographic Location: USA
Subfile: AHSearch
Journal Subject Category: CHEMISTRY, MULTIDISCIPLINARY

- end of record -

? d s3/3/1
Display 3/3/1 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

12792619 EMBASE No: 2004380132
Nanoparticle and targeted systems for cancer therapy
Brannon-Peppas L.; Blanchette J.O.
L. Brannon-Peppas, Department of Biomedical Engineering, The University of Texas at Austin, 1 Univ. Station, C0800, 78712-0231, Austin, TX United States
AUTHOR EMAIL: peppas@mail.utexas.edu
Advanced Drug Delivery Reviews (ADV. DRUG DELIV. REV.) (Netherlands) 22 SEP 2004, 56/11 (1649-1659)
CODEN: ADDRE ISSN: 0169-409X
PUBLISHER ITEM IDENTIFIER: S0169409X04001450
DOCUMENT TYPE: Journal ; **Review**
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 43

- end of record -

? d s9/3/43
Display 9/3/43 (Item 1 from file: 484)
DIALOG(R)File 484:Periodical Abs Plustext

05030542 SUPPLIER NUMBER: 71514165 (USE FORMAT 7 OR 9 FOR FULLTEXT)
Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements
Setchell, Kenneth D R; Brown, Nadine M; Desai, Pankaj; Zimmer-Nechemias, Linda; Et al
Journal of Nutrition (IJNU), v131 n4S, pS1362-S1375, p.14
Apr 2001
ISSN: 0022-3166 JOURNAL CODE: IJNU
DOCUMENT TYPE: Feature
LANGUAGE: English RECORD TYPE: Fulltext; Abstract
WORD COUNT: 10845

- end of record -

? d s13/3/12,13,15

Display 13/3/12 (Item 1 from file: 440)

DIALOG(R)File 440:Current Contents Search(R)

16392292 Document Delivery Available: 000183613000014 References: 28
TITLE: Identification of CYP1A2 as the main isoform for the phase I hydroxylated metabolism of genistein and a prodrug **converting enzyme of methylated** isoflavones
AUTHOR(S): Hu M (REPRINT); Krausz K; Chen J; Ge X; Li JQ; Gelboin HL; Gonzalez FJ
AUTHOR(S) E-MAIL: minghu@wsu.edu
CORPORATE SOURCE: Washington State Univ, Dept Pharmaceut Sci, /Pullman//WA/99164 (REPRINT); Washington State Univ, Dept Pharmaceut Sci, /Pullman//WA/99164; NCI, NIH, /Bethesda//MD/20892; NCI, NIH, /Bethesda//MD/20892; Shanghai Inst Pharmaceut Ind, Dept Med Chem, /Shanghai//Peoples R China/
PUBLICATION TYPE: JOURNAL
PUBLICATION: DRUG METABOLISM AND DISPOSITION, 2003, V31, N7 (JUL), P924-931
GENUINE ARTICLE#: 691NU
PUBLISHER: AMER SOC PHARMACOLOGY EXPERIMENTAL THERAPEUTICS, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998 USA
ISSN: 0090-9556
LANGUAGE: English DOCUMENT TYPE: ARTICLE (ABSTRACT AVAILABLE)

- end of record -

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Display 13/3/13 (Item 1 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

01672908
5-ALKYL-7-ALKYLCARBONATE- ISOFLAVONE **ESTER AS** ISOFLAVONE PRODRUG
ESTER DE 5-ALKYL-7-ALKYLCARBONATE-ISOFLAVONE EN TANT QUE PROMEDICAMENT A BASE D'ISOFLAVONE
PATENT ASSIGNEE:
Biotest Laboratories, LLC, (4581490), P.O. Box 60310, 1850 Reliable Circle, Colorado Springs, CO 80960, (US), (Applicant designated States: all)
INVENTOR:
ROBERTS, William, J., 12391 S.E. 138 Avenue, Oklawaha, FL 32179, (US)
PATENT (CC, No, Kind, Date): WO 2003087083 031023
APPLICATION (CC, No, Date): EP 2003746754 030411; WO 2003US11424 030411
PRIORITY (CC, No, Date): US 123068 020412
DESIGNATED STATES: AT; BE; BG; CH; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HU; IE; IT; LI; LU; MC; NL
EXTENDED DESIGNATED STATES: AL; LT; LV; MK
INTERNATIONAL PATENT CLASS: C07D-311/36; A61K-031/35; A61P-021/06
LANGUAGE (Publication,Procedural,Application): English; English; English

- end of record -

?

Display 13/3/15 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10842072 Genuine Article#: 564CE No. References: 0
Title: Isoflavone prodrugs **as glioblastoma inhibitors**
Author(s): Bhushan A; Lynch L; Adejare A
Corporate Source: Idaho State Univ,Coll Pharm, Dept Pharmaceut Sci,Pocatello//ID/83209
Journal: ABSTRACTS OF PAPERS OF THE AMERICAN CHEMICAL SOCIETY, 2002, V223, 2 (APR 7), PB132-B132
ISSN: 0065-7727 Publication date: 20020407
Publisher: AMER CHEMICAL SOC, 1155 16TH ST, NW, WASHINGTON, DC 20036 USA
Language: English Document Type: MEETING ABSTRACT

- end of record -

? ds

Set	Items	Description
S1	1007	(ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES OR DIHYDROISOFLAVONE OR DAIDZEIN OR GENISTEIN OR GLYCITEIN) - AND (PRODRUG OR PRODRUGS OR PRO()DRUG OR PRO()DRUGS)
S2	3	S1 AND DT=REVIEW
S3	3	RD (unique items)
S4	4867	(PRODRUG OR PRODRUGS) AND DT=REVIEW
S5	2	S4 AND (DAIDZEIN OR GENISTEIN OR GLYCITEIN)
S6	2	RD (unique items)
S7	74	(DAIDZEIN OR GENISTEIN OR GLYCITEIN)(10N)(PRODRUG OR PRODR-UGS)
S8	66	RD (unique items)
S9	48	S8 AND (CANCER)
S10	0	(ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES OR DIHYDROISOFLAVONE)(10N)(PRODRUG OR PRODRUGS OR PRO()DRUG - OR PRO()DRUGS) AND DT=REVIEW
S11	0	(ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES OR DIHYDROISOFLAVONE)(20N)(PRODRUG OR PRODRUGS OR PRO()DRUG - OR PRO()DRUGS) AND DT=REVIEW
S12	36	(ISOFLAVONOID OR ISOFLAVONE OR ISOFLAVONOIDS OR ISOFLAVONES OR DIHYDROISOFLAVONE)(10N)(PRODRUG OR PRODRUGS OR PRO()DRUG - OR PRO()DRUGS)
S13	21	RD (unique items)

? bye
01feb05 17:45:06 User276646 Session D73.3
$4.73 0.802 DialUnits File654
$21.00 30 Type(s) in Format 3
$21.00 30 Types
$25.73 Estimated cost File654
$20.37 4.289 DialUnits File349
$33.60 21 Type(s) in Format 3
$25.00 4 Type(s) in Format 7
$58.60 25 Types
$78.97 Estimated cost File349
$35.41 1.540 DialUnits File440
$12.52 2 Type(s) in Format 3
$6.26 1 Type(s) in Format 7
$18.78 3 Types
$54.19 Estimated cost File440

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           $3.15  1 Type(s) in Format  2
           $6.80  4 Type(s) in Format  3
        $9.95  5 Types
$14.57  Estimated cost File348
        $1.82    0.107 DialUnits File340
           $2.16  1 Type(s) in Format  3
           $1.51  1 Type(s) in Format 42
        $3.67  2 Types
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       $26.53    2.495 DialUnits File73
          $23.52  8 Type(s) in Format  3
           $8.82  3 Type(s) in Format  7
           $2.94  1 Type(s) in Format  9
       $35.28  12 Types
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 $0.00  Estimated cost File390
       $21.39    0.966 DialUnits File34
          $12.86  2 Type(s) in Format  3
           $6.43  1 Type(s) in Format  7
           $6.43  1 Type(s) in Format  9
       $25.72  4 Types
$47.11  Estimated cost File34
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 $0.96  Estimated cost File5
        $0.92    0.289 DialUnits File155
 $0.92  Estimated cost File155
        $1.52    0.282 DialUnits File148
           $1.55  1 Type(s) in Format  3
        $1.55  1 Types
 $3.07  Estimated cost File148
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 $0.48  Estimated cost File156
        $0.74    0.059 DialUnits File399
 $0.74  Estimated cost File399
        $0.07    0.010 DialUnits File453
 $0.07  Estimated cost File453
        $0.47    0.086 DialUnits File16
 $0.47  Estimated cost File16
        $0.22    0.026 DialUnits File71
 $0.22  Estimated cost File71
        $1.05    0.273 DialUnits File144
           $1.65  1 Type(s) in Format  3
        $1.65  1 Types
 $2.70  Estimated cost File144
        $0.28    0.056 DialUnits File324
 $0.28  Estimated cost File324
        $0.50    0.084 DialUnits File545
 $0.50  Estimated cost File545
        $0.17    0.169 DialUnits File20
 $0.17  Estimated cost File20
        $0.20    0.056 DialUnits File94
 $0.20  Estimated cost File94
        $0.07    0.012 DialUnits File135
 $0.07  Estimated cost File135
       $13.74    2.804 DialUnits File484
```

```
          $4.50  3 Type(s) in Format  3
          $3.40  1 Type(s) in Format  7
        $7.90  4 Types
$21.64  Estimated cost File484
        $0.02    0.022 DialUnits File610
 $0.02  Estimated cost File610
        $0.21    0.039 DialUnits File621
 $0.21  Estimated cost File621
        $0.24    0.044 DialUnits File649
 $0.24  Estimated cost File649
        $0.13    0.029 DialUnits File50
 $0.13  Estimated cost File50
        $0.08    0.019 DialUnits File162
 $0.08  Estimated cost File162
        $6.62    0.315 DialUnits File357
          $4.90  2 Type(s) in Format  3
        $4.90  2 Types
$11.52  Estimated cost File357
        $0.21    0.039 DialUnits File636
 $0.21  Estimated cost File636
        $0.16    0.030 DialUnits File9
 $0.16  Estimated cost File9
        $0.14    0.026 DialUnits File15
 $0.14  Estimated cost File15
        $0.30    0.074 DialUnits File35
          $1.20  1 Type(s) in Format  3
        $1.20  1 Types
 $1.50  Estimated cost File35
        $0.09    0.009 DialUnits File107
 $0.09  Estimated cost File107
        $0.16    0.036 DialUnits File149
 $0.16  Estimated cost File149
        $0.11    0.010 DialUnits File172
 $0.11  Estimated cost File172
        $0.08    0.018 DialUnits File211
 $0.08  Estimated cost File211
        $0.23    0.043 DialUnits File345
          $10.55  1 Type(s) in Format  3
       $10.55  1 Types
$10.78  Estimated cost File345
        $0.00    0.013 DialUnits File391
 $0.00  Estimated cost File391
        $0.05    0.007 DialUnits File441
 $0.05  Estimated cost File441
        $0.79    0.080 DialUnits File452
          $14.40  2 Type(s) in Format  3
       $14.40  2 Types
$15.19  Estimated cost File452
        $0.03    0.014 DialUnits File553
 $0.03  Estimated cost File553
        $0.11    0.021 DialUnits File635
 $0.11  Estimated cost File635
        $0.22    0.030 DialUnits File759
          $2.65  1 Type(s) in Format  3
        $2.65  1 Types
 $2.87  Estimated cost File759
        $0.40    0.055 DialUnits File761
```

```
          $2.65  1 Type(s) in Format  3
        $2.65  1 Types
   $3.05  Estimated cost File761
          OneSearch, 45 files, 16.669 DialUnits FileOS
   $8.53  TELNET
 $375.62  Estimated cost this search
 $395.05  Estimated total session cost  24.106 DialUnits

Logoff: level 04.20.00 D  17:45:06

You are now logged off
```